National Clinical Guideline Centre

Intravenous fluid therapy

Intravenous fluid therapy in adults in hospital

Clinical Guideline <CG174>

Methods, evidence and recommendations

December 2013

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The Royal College of Surgeons of England

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April 2017: Key research recommendations 2 to 4 have been stood down and deleted from the short version of this guideline. These recommendations have been greyed out in this document.

December 2016: A footnote was added to recommendations 19 and 22, tables 4.2.3 and 4.2.4 and the algorithms giving more information on weight-based potassium prescriptions.

October 2016: A correction was made to the IV fluid therapy algorithm to clarify the period of time over which a fluid bolus can be given. A missing entry was corrected in the table showing the composition of commonly used crystalloids.

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Guideline development group members

Name	Role
Michael Stroud	Chair, Consultant in Gastro-enterology and General (internal) medicine, Southampton University
Reem Al-Jayyousi	Consultant Nephrologist
Paul Cook	Consultant in Chemical Pathology
Richard Leach	Consultant in Respiratory and Critical care
Dileep Lobo	Professor of Gastrointestinal Surgery
Tom McLoughlin-Yip	Patient and carer member
Michael Mythen	Professor of Anaesthetics and Critical care (until October 2012)
Patrick Nee	Consultant in Emergency Medicine and Critical care medicine
Jerry Nolan	Consultant in Intensive care and Anaesthetics (from October 2012)
Fleur North	Patient and carer member
Katie Scales	Consultant Nurse- Critical care (Outreach)
Rebecca Sherratt	Advanced Nurse Practitioner
Neil Soni	Consultant in Intensive care and Anaesthetics
Mark Tomlin	Consultant Pharmacist – Critical care

Expert advisors to the group

Name	Role
Andrew Lewington	Consultant Nephrologist, GDG member from Acute Kidney Injury guideline
Michael Mythen	Professor of Anaesthetics and Critical care (from October 2012)

National Clinical Guideline Centre technical team

Name	Role
Joanna Ashe	Senior Information Scientist
Ian Bullock	Guideline Lead (from November 2011)
Varo Kirthi	Co-opted Technical Team Member
Lilian Li	Health Economist
Smita Padhi	Senior Research Fellow and Project Manager
David Wonderling	Health Economics Lead
Nina Balachander	Senior Research Fellow (from March 2013 to April 2013)
Serena Carville	Senior Research Fellow (from February 2013 until March 2013)
Lee Yee Chong	Senior Research Fellow (from July 2011 until November 2012)
Jennifer Layden	Senior Project Manager (from July 2011 until July 2012)
Julie Neilson	Senior Research Fellow and Project manager (from December 2010 until July 2011)
Sara Buckner	Research Fellow (from July 2011 until April 2012)
Susan Latchem	Guideline lead/Operations director (from December 2010 until November 2011)

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NCGC:
Maggie Westby, Clinical Effectiveness Lead, NCGC
Hati Zorba, Project Co-ordinator, NCGC
Jill Cobb, Information Scientist, NCGC
Sarah Hodgkinson, Senior Research Fellow and Project Manager, NCGC

NICE Project team:
Sharon Summers-Ma, Associate Director
Mark Baker, Clinical Adviser
Claire Ruiz, Guideline Commissioning Manager, NICE (from May 2013)
Clifford Middleton, Guideline Commissioning Manager, NICE (until May 2013)
Elaine Clydesdale, Guideline Coordinator
Steven Barnes, Technical Lead
Jasdeep Hayre, Health Economist
Sarah Palombella, Senior Medical Editor

1 Introduction

Many adult hospital inpatients need intravenous (IV) fluid therapy to prevent or correct problems with their fluid and/or electrolyte status. This may be because they cannot meet their normal needs through oral or enteral routes (for example, they have swallowing problems or gastrointestinal dysfunction) or because they have unusual fluid and/or electrolyte deficits or demands caused by illness or injury (for example, high gastrointestinal or renal losses). Deciding on the optimal amount and composition of IV fluids to be administered and the best rate at which to give them can be a difficult task, and decisions must be based on careful assessment of the patient's individual needs.

Despite the relative complexity of estimating a patient's IV fluid needs, assessment and prescription is often delegated to healthcare professionals who have received little or no specific training on the subject. Indeed, the task of prescribing IV fluids is often left to the most junior medical staff, who frequently lack the relevant experience. This problem was highlighted by a 1999 National Confidential Enquiry into Perioperative Deaths (NCEPOD) report, which found that a significant number of hospitalised patients were dying as a result of the infusion of too much or too little fluid.[73] The report then recommended that fluid prescribing should be given the same status as drug prescribing. Unfortunately this has not yet occurred, and although inappropriate fluid therapy is rarely reported as being responsible for patient harm, it remains likely that as many as 1 in 5 patients on IV fluids and electrolytes suffer complications or morbidity due to their inappropriate administration.

Errors in prescribing IV fluids and electrolytes are particularly likely in emergency departments, acute admission units, and general medical and surgical wards rather than in operating theatres and critical care units because patients in more general areas usually have less cardiovascular monitoring and the staff may have less experience of fluid prescribing. Indeed, surveys have shown that many staff who prescribe IV fluids in such areas know neither the likely fluid and electrolyte needs of individual patients, nor the specific composition of the many choices of IV fluids available to them. Standards of recording and monitoring IV fluid and electrolyte therapy may also be poor in these settings, and staff may fail to reassess and respond to patients' inevitable changes in IV fluid and electrolyte status over time.

In addition to the problems above, there is also considerable debate among IV fluid and electrolyte experts about the best IV fluids to use, particularly for more seriously ill or injured patients. There is therefore wide variation in clinical practice. Many reasons underlie the ongoing debate, but most revolve around difficulties in interpretation of both trials evidence and clinical experience, including the following factors:

- Many accepted practices of IV fluid prescribing were developed for historical reasons rather than through clinical trials.
- Trials cannot easily be included in meta-analyses because they examine varied outcome measures in heterogeneous groups, comparing not only different types of fluid with different electrolyte content, but also different volumes and rates of administration and, in some cases, the additional use of inotropes or vasopressors.
- Most trials have been undertaken in operating theatres and critical care units rather than admission units or general and elderly care settings.
- Trials claiming to examine best early therapy for resuscitation have actually evaluated therapy choices made after initial resuscitation with patients already in critical care or operating theatres.
- Many trials inferring best therapy for resuscitation after acute fluid loss have actually examined situations of hypovolaemia induced by anaesthesia.

In the light of all the above, there is a clear need for guidance on IV fluid therapy for general areas of hospital practice, covering both the prescription and monitoring of IV fluid and electrolyte therapy, and the training and educational needs of all hospital staff involved in IV fluid management.

The aim of this NICE guideline is therefore to help prescribers understand the:

- physiological principles that underpin fluid prescribing
- pathophysiological changes that affect fluid balance in disease states
- indications for IV fluid therapy
- reasons for the choice of the various fluids available and
- principles of assessing fluid balance.

In developing the guideline, however, it was necessary to limit the scope by excluding patient groups with more specialised fluid prescribing needs. It is important to emphasise from the outset that the recommendations do not apply to patients under 16 years, pregnant women, and those with severe liver or renal disease, diabetes or burns. They also do not apply to patients needing inotropes and those on intensive monitoring, and so they have less relevance to intensive care settings and patients during surgical anaesthesia. Patients with traumatic brain injury (including neurosurgical patients) are also excluded and the recommendations do not cover the actual administration (as opposed to the prescription) of IV fluids.

It is hoped that this guideline will lead to better fluid prescribing in hospitalised patients, help reduce both morbidity and mortality, and lead to better patient outcomes.

Strategies for further research into the subject have also been proposed.

2 Development of the guideline

2.1 What is a NICE clinical guideline?

NICE clinical guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances within the NHS – from prevention and self-care through primary and secondary care to more specialised services. We base our clinical guidelines on the best available research evidence, with the aim of improving the quality of health care. We use predetermined and systematic methods to identify and evaluate the evidence relating to specific review questions.

NICE clinical guidelines can:

- provide recommendations for the treatment and care of people by health professionals
- be used to develop standards to assess the clinical practice of individual health professionals
- be used in the education and training of health professionals
- help patients to make informed decisions
- improve communication between patient and health professional

While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills.

We produce our guidelines using the following steps:

- Guideline topic is referred to NICE from the Department of Health
- Stakeholders register an interest in the guideline and are consulted throughout the development process.
- The scope is prepared by the National Clinical Guideline Centre (NCGC)
- The NCGC establishes a guideline development group
- A draft guideline is produced after the group assesses the available evidence and makes recommendations
- There is a consultation on the draft guideline.
- The final guideline is produced.

The NCGC and NICE produce a number of versions of this guideline:

- the full guideline contains all the recommendations, plus details of the methods used and the underpinning evidence
- the NICE guideline lists the recommendations
- information for the public is written using suitable language for people without specialist medical knowledge
- the NICE pathway brings together all connected NICE guidance.

This version is the full version. The other versions can be downloaded from NICE at www.nice.org.uk

2.2 Remit

NICE received the remit for this guideline from the Department of Health. They commissioned the NCGC to produce the guideline.

The remit for this guideline is:

To produce a clinical guideline on intravenous fluid therapy in hospitalised adult patients.

2.3 Who developed this guideline?

A multidisciplinary Guideline Development Group (GDG) comprising professional group members and consumer representatives of the main stakeholders developed this guideline (see section on Guideline Development Group Membership and acknowledgements).

The National Institute for Health and Care Excellence funds the National Clinical Guideline Centre (NCGC) and thus supported the development of this guideline. The GDG was convened by the NCGC and chaired by Michael Stroud in accordance with guidance from the National Institute for Health and Care Excellence (NICE).

The group met every 5-6 weeks during the development of the guideline. At the start of the guideline development process all GDG members declared interests including consultancies, fee-paid work, share-holdings, fellowships and support from the healthcare industry. At all subsequent GDG meetings, members declared arising conflicts of interest, which were also recorded (Appendix B)

Members were either required to withdraw completely or for part of the discussion if their declared interest made it appropriate. The details of declared interests and the actions taken are shown in Appendix B.

Staff from the NCGC provided methodological support and guidance for the development process. The team working on the guideline included a project manager, systematic reviewers, health economists and information scientists. They undertook systematic searches of the literature, appraised the evidence, conducted meta-analysis and cost effectiveness analysis where appropriate and drafted the guideline in collaboration with the GDG.

2.4 What this guideline covers

This guideline covers the following populations:

Adults (16 years and older) in hospital receiving intravenous fluid therapy

The following clinical issues are covered:

- Training and education in clinical assessment, prescribing, monitoring, evaluating and documenting intravenous fluid therapy in hospitals.
- Assessment, monitoring and re-evaluation of fluid and electrolyte status
- Appropriate documentation for clinical assessment, prescribing, monitoring and re-evaluation of the patient's fluid and electrolyte status.
- Types, volume and timing of fluids and electrolytes to restore fluid balance (resuscitation):
  - crystalloids compared with other crystalloids
  - crystalloids compared with colloids
  - colloids compared with other colloids.
- Types, volume and timing of fluids and electrolytes to maintain fluid balance:
  - crystalloids compared with other crystalloids.
- Types, volume and timing of fluids and electrolytes to replace continuing abnormal fluid losses:
  - crystalloids compared with other crystalloids
  - crystalloids compared with colloids
  - colloids compared with other colloids.
- Specific considerations related to intravenous fluid therapy in patients who have:
  - acute kidney injury, up to the point of renal replacement therapy

- sepsis
- trauma
- congestive heart failure.

For further details please refer to the scope in Appendix A and review questions in section 3.1.

2.5 What this guideline does not cover

The guideline does not cover the following:

Populations:

- People younger than 16 years.
- Pregnant women.
- Patients with severe (stage 4 or 5) chronic kidney disease or liver disease (Child-Pugh grade A-C).
- Patients with diabetes, including those with diabetic ketoacidosis and hyperosmolar states.
- Patients needing inotropes to support their circulation.
- Patients with burns.
- Patients with traumatic brain injury or needing neurosurgery.

Key areas:

- Route of administration and intravenous catheter-related issues, such as choice of catheter, placement techniques and catheter-related infection.
- Use of blood and blood products, except albumin.
- The specific monitoring or prescription of electrolytes, minerals and trace elements other than sodium, potassium and chloride, unless their status directly influences sodium, potassium or chloride provision (for example, low magnesium preventing correction of hypokalaemia).
- Use of inotropes to support circulatory failure.
- Invasive monitoring of fluid status, for example in critical care or during surgical anaesthesia.
- Parenteral nutrition beyond consideration of fluid and electrolyte content.
- Labelling, preparation and storage of both standard and non-standard intravenous fluids.
- Ethical issues related to intravenous fluid prescription at the end of life.

2.6 Relationships between the guideline and other NICE guidance

Related NICE Health Technology Appraisals:

Pre-hospital initiation of fluid replacement therapy in trauma. NICE technology appraisal guidance 74 (2004).

Related NICE Clinical Guidelines:

Acute kidney injury. NICE clinical guideline 169 (2013).

Patient experience in adult NHS services. NICE clinical guideline and quality standard (2012).

Chronic Kidney Disease. NICE clinical guideline 73 (2008). This guidance is currently being updated.

Medicines adherence. NICE clinical guideline 76 (2009).

Acutely ill patients in hospital. NICE clinical guideline 50 (2007).

Obesity. NICE clinical guideline 43 (2006)

Nutrition support in adults. NICE clinical guideline 32 (2006).

Type 1 diabetes. NICE clinical guideline 15 (2004).

Related NICE Public Health Guidance:

Prevention and control of healthcare associated infections. NICE public health quality improvement guide 36 (2011).

NICE Related Guidance currently in development:

Transfusion. NICE clinical guideline. Publication expected May 2015.

Major trauma: Assessment and management of major trauma. NICE clinical guideline. Publication expected June 2015.

Intravenous fluid therapy in children. NICE clinical guideline. Publication expected November 2015.

Type 1 Diabetes (update). NICE clinical guideline. Publication expected August 2015.

3 Methods

This guidance was developed in accordance with the methods outlined in the NICE Guidelines Manual 2009.[76] An updated NICE Guidelines Manual was published in 2012, when this guideline was already in development.

3.1 Developing the review questions and outcomes

Review questions were developed in a PICO framework (patient, intervention, comparison and outcome) for intervention reviews. This was to guide the literature searching process and to facilitate the development of recommendations by the guideline development group (GDG). These were drafted by the NCGC technical team and refined and validated by the GDG. The questions were based on the key clinical areas identified in the scope (see Appendix A).

Due to the breadth of the scope and the target population, the GDG often found that several review questions could be generated for a single area within the scope. However, only 15 to 20 questions can be reasonably managed within the usual time frame of full clinical guideline development (18 months). Since it was not possible to cover all potentially important aspects, the GDG considered the relative importance of these and prioritised areas for developing review questions [77]. This decision to prioritise certain areas took into consideration factors such as whether the area is a key clinical issue for the NHS, patient safety, cost (to the NHS), equality and variations in practice.

Table 1: Review questions

Chapter	Review questions	Outcomes
Principles and protocols of intravenous fluid therapy	What is the clinical and cost effectiveness of clinical algorithms or defined protocols for the assessment, monitoring and/or management of intravenous fluid and electrolyte requirement in hospitalised adult patients?	• All-cause mortality within 30 days of hospitalisation • Length of stay in hospital • Length of stay in Intensive care unit • Quality of life • Renal complications • Pulmonary oedema
Assessment and monitoring on intravenous fluid therapy	What aspects of clinical assessment are required to assess, monitor and re-evaluate fluid and electrolyte status?	N/A
	In hospitalised patients receiving intravenous fluids, what is the clinical and cost effectiveness of measuring and recording serial body weight?	• All-cause mortality within 30 days of hospitalisation • Length of stay in hospital • Length of stay in intensive care unit • Quality of life • Renal complications/Acute Kidney Injury defined as an increase of 50% or more of serum creatinine from baseline • Respiratory complications including pulmonary oedema, respiratory failure, chest infection, mechanical ventilation • Morbidity – measured by SOFA

Chapter	Review questions	Outcomes
		(Sequential Organ Failure Assessment) score and Multiple Organ Dysfunction Score (MODS). • Total volume of fluid received (if both groups receive the same type of fluid).
	In hospitalised patients receiving intravenous fluids, what is the clinical and cost effectiveness of measuring and recording urine output in addition to recording standard parameters stated in NEWS (National Early Warning Score) to determine the need for intravenous fluid administration?	• All-cause mortality within 30 days of hospitalisation • Length of stay in hospital • Length of stay in intensive care unit • Quality of life • Renal complications/Acute Kidney Injury defined as an increase of 50% or more of serum creatinine from baseline • Respiratory complications including pulmonary oedema, respiratory failure, chest infection, mechanical ventilation • Morbidity – measured by SOFA (Sequential Organ Failure Assessment) score and Multiple Organ Dysfunction Score (MODS). • Total volume of fluid received (if both groups receive the same type of fluid).
	In hospitalised patients receiving intravenous fluids, what is the incidence and clinical significance of hyperchloraemia and hypochloraemia?	• All-cause mortality • Length of stay in hospital and/or intensive care unit • Quality of life • Renal complications/Acute Kidney Injury (AKI) defined as an increase of 50% or more of serum creatinine from baseline level • Morbidity – measured by SOFA (Sequential Organ Failure Assessment) score and Multiple Organ Dysfunction Score (MODS). • Hyperchloraemia • Hyperchloraemic acidosis • Hypochloraemia.
Intravenous fluid therapy for resuscitation	What is the most clinically and cost effective intravenous fluid for fluid resuscitation of hospitalised patients?	• All-cause mortality within 30 days of hospitalisation • Length of stay in hospital • Length of stay in intensive care

Chapter	Review questions	Outcomes
		unit • Quality of life • Renal complications/Acute Kidney Injury defined as an increase of 50% or more in serum creatinine level from baseline • Respiratory complications including pulmonary oedema, respiratory failure, chest infection and mechanical ventilation • Morbidity – measured by SOFA (Sequential Organ Failure Assessment) score and Multiple Organ Dysfunction Score (MODS).
	What is clinical and cost effectiveness of different volumes of intravenous fluid administration for fluid resuscitation? What are the most clinically and cost effective timing and rate of administration of intravenous fluids for fluid resuscitation?	• All-cause mortality within 30 days of hospitalisation • Length of stay in hospital • Length of stay in intensive care unit • Quality of life • Renal complications/Acute Kidney Injury defined as an increase of 50% or more in serum creatinine level from baseline • Respiratory complications including pulmonary oedema, respiratory failure, chest infection, mechanical ventilation • Morbidity – measured by SOFA (Sequential Organ Failure Assessment) score and Multiple Organ Dysfunction Score (MODS).
Intravenous fluid therapy for routine maintenance	What is the most clinically and cost effective intravenous fluid for routine maintenance in hospitalised patients?	• All-cause mortality within 30 days of hospitalisation • Length of stay in hospital • Length of stay in intensive care unit • Quality of life • Renal complications/Acute Kidney Injury defined as an increase of 50% or more in serum creatinine level from baseline • Respiratory complications including pulmonary oedema , respiratory failure, chest

Chapter	Review questions	Outcomes
		infection, mechanical ventilation • Morbidity – measured by SOFA (Sequential Organ Failure Assessment) score and Multiple Organ Dysfunction Score (MODS).
	What is clinical and cost effectiveness of different volumes of intravenous fluid administration for routine maintenance? What is the most clinically and cost effective timing and rate of administration of intravenous fluids for routine maintenance?	• All-cause mortality within 30 days of hospitalisation • Length of stay in hospital • Length of stay in intensive care unit • Quality of life • Renal complications/Acute Kidney Injury defined as an increase of 50% or more in serum creatinine level from baseline • Respiratory complications including pulmonary oedema, respiratory failure, chest infection and mechanical ventilation • Morbidity – measured by SOFA (Sequential Organ Failure Assessment) score and Multiple Organ Dysfunction Score (MODS).
Intravenous fluid therapy for replacement and redistribution	What is the most clinically and cost effective intravenous fluid for replacement of abnormal ongoing losses in hospitalised patients?	• All-cause mortality within 30 days of hospitalisation • Length of stay in hospital • Length of stay in intensive care unit • Quality of life • Renal complications/Acute Kidney Injury defined as an increase of 50% or more in serum creatinine level from baseline • Respiratory complications including pulmonary oedema, respiratory failure, chest infection and mechanical ventilation • Morbidity – measured by SOFA (Sequential Organ Failure Assessment) score and Multiple Organ Dysfunction Score (MODS).
	What is clinical and cost effectiveness of different volumes of intravenous fluid administration for replacement of	• All-cause mortality within 30 days of hospitalisation • Length of stay in hospital

Chapter	Review questions	Outcomes
	abnormal ongoing losses? What is the most clinically and cost effective timing and rate of administration of intravenous fluids for replacement of abnormal ongoing losses?	• Length of stay in intensive care unit • Quality of life • Renal complications/Acute Kidney Injury defined as an increase of 50% or more in serum creatinine level from baseline • Respiratory complications including pulmonary oedema, respiratory failure, chest infection and mechanical ventilation • Morbidity – measured by SOFA (Sequential Organ Failure Assessment) score and Multiple Organ Dysfunction Score (MODS).
Training and education for management of intravenous fluid therapy	What are the barriers faced by healthcare professionals in the effective prescription and monitoring of intravenous fluids in hospital settings?	• Health care professionals' views and experiences.

3.1.1 Issues with evidence related to guideline

Early in the development of the guideline it was identified that evidence from multiple groups of patients would need to be considered due to the breadth of the target population. However, the evidence from one group of patients was not necessarily applicable to all hospitalised patients as these groups have different fluid requirement and responses to intravenous fluid therapy. This was a recurring feature with the majority of the evidence identified for this guideline.

The other important issues which came to light during development were:

- Lack of evidence: Except for some areas in the guideline, there was a lack of evidence, especially high quality evidence from randomised controlled trials (RCTs) and large cohort studies with respect to intravenous fluid therapy
- Fraudulent research: A large number of trials pertaining to the types and administration of intravenous fluids had been retracted during the guideline's development period or were under investigation for retraction.

3.1.2 Review strategy

A robust but pragmatic approach was warranted in the absence of high quality evidence.

3.1.2.1 Indirect evidence

When RCT evidence was not available, the initial approach was to consider using indirect evidence from RCTs in other populations - evidence from one subgroup that could be extrapolated to others. The GDG members discussed the applicability of the evidence across groups and situations where indirect evidence informed decision making and these were explicitly documented.

For example , the target population for the review on fluid resuscitation was adults in hospital who were receiving intravenous fluid therapy for fluid resuscitation. The GDG discussed and agreed that if

no evidence in the target population was identified, the review would include indirect evidence in the following order:

1.patients in intensive care units/ high dependency units,

2.emergency services, including patients fluid resuscitation in ambulances and emergency services

3.intra-operative patients (this would however exclude patients receiving IV fluids for normovolaemic hemodilution, intraoperative cardiac bypass surgery and preload for spinal anaesthesia as these were deemed to be too indirect or relevant to the target population)

3.1.2.2 Evidence from non-randomised studies

It was highlighted that evidence from RCTs was only available for selected clinical questions, and the GDG agreed on a consistent approach to include non-randomised studies in this guideline.

However, the breadth of population of the guideline meant that the fine balance of investing more resources to search and evaluate lower quality evidence from observational studies was to be carefully evaluated against the additional value it brought to the decision making process.

Therefore, the review strategy for inclusion of evidence from RCTs and non-randomised studies followed the following principles in a step wise manner:

- Only randomised controlled trials were included, if evidence was available (for review questions relating to interventions)
- Prospective cohort studies were included if the following conditions were met:
  - No RCT evidence available
  - Evidence available from RCTs where only limited to specific populations within the clinical question, and it was considered inappropriate to extrapolate the information to other subgroups.
  - There were controversies regarding the best practice in the area – the GDG were uncomfortable in making recommendations based on consensus and believed that even very low quality evidence may provide relevant information that impacted their decisions.

3.1.2.3 Fraudulent research

A decision was taken by the GDG to exclude any study that had been retracted or was under investigation. The majority of these studies had contributions by Joachim Boldt.

3.1.2.4 Studies conducted before 1990

The GDG discussed that there have been considerable changes in clinical practice in the past few decades, with the implication that older studies may not be applicable. This was taken into account when deciding the review protocols and studies published before 1990 were excluded for the reviews where this would have an impact (fluid resuscitation)

3.1.2.5 Recommendations based on consensus

It was acknowledged that it was not possible to undertake clinical evidence reviews for certain areas of the guideline. Two such areas which were exceptions to the normal systematic review process were:

- standard principles of intravenous fluid therapy
- assessment and monitoring of intravenous fluid and electrolyte needs

Here, the GDG took into consideration the principles of physiology and pathophysiology of intravenous fluids and other accepted standard clinical guidance and drafted recommendations based on expert consensus in a format intended to be useful to a clinician. [16,95]

The National Early Warning Score (NEWS) is a Department of Health initiative which was accepted by the GDG as a reliable and informative scoring system for assessment. The GDG based this decision on the fact that NEWS has been demonstrated to be as good as the best of other early warning scores in discriminating risk of acute mortality and is likely to be more sensitive than most currently used systems at prompting an alert and clinical response to acute illness deterioration.[95]

3.2 Searching for evidence

3.2.1 Clinical literature search

Systematic literature searches were undertaken to identify evidence within published literature in order to answer the review questions as per The Guidelines Manual [2009].[76] Clinical databases were searched using relevant medical subject headings, free-text terms and study type filters where appropriate. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English language. All searches were conducted on core databases, MEDLINE, Embase and The Cochrane Library. Additional subject specific databases were used for some questions: CINAHL for questions on training and education, algorithms, urine output, and daily weights; PsycINFO for the training and education question. All searches were updated on 12 March 2013. No papers after this date were considered.

Search strategies were checked by looking at reference lists of relevant key papers, checking search strategies in other systematic reviews and asking the GDG for known studies. The questions, the study types applied, the databases searched and the years covered can be found in Appendix D.

This is a clinical area that presented challenges when searching for the evidence. There was no clear population for each question, as well as a lack of consistency in the terminology used in the papers and in the application of index terms in the databases. These factors tend to lead to very large searches with imprecise retrieval. There was a need to balance this with the resources available to sift through large retrievals within the time allotted. For this reason there was extra reliance on finding evidence through methods such as checking reference lists or asking the GDG for known studies, as a supplement to the literature searches. This is in line with methodology suggested by the Cochrane Collaboration.[2]

As an extra precaution, reviewers also checked through the all studies which were ordered but excluded for related reviews, to ensure that no relevant studies were missed. For example, when looking for studies for the volume and timing of resuscitation review, reviewers also checked the studies which had been ordered for the algorithm questions (there is a possibility that some algorithms effectively compare early vs. late resuscitation) and the fluid type question.

During the scoping stage, a search was conducted for guidelines and reports on the websites listed below and on organisations relevant to the topic. Searching for grey literature or unpublished literature was not undertaken. All references sent by stakeholders were considered.

- Guidelines International Network database (www.g-i-n.net)
- National Guideline Clearing House (www.guideline.gov/)
- National Institute for Health and Care excellence (NICE) (www.nice.org.uk)
- National Institutes of Health Consensus Development Program (consensus.nih.gov/)
- National Library for Health (www.library.nhs.uk/)

3.2.2 Health economic literature search

Systematic literature searches were also undertaken to identify health economic evidence within published literature relevant to the review questions. The evidence was identified by conducting

broad searches relating to specific key areas in the NHS economic evaluation database (NHS EED), the Health Economic Evaluations Database (HEED) and health technology assessment (HTA) databases with no date restrictions. Additionally, the searches were run on MEDLINE and Embase, with a specific economic filter to ensure publications that had not yet been indexed by these databases were identified. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English language.

The search strategies for health economics are included in Appendix D. All searches were updated on 12 March 2013. No papers published after this date were considered.

3.3 Evidence of effectiveness

The Research Fellow:

- Identified potentially relevant studies for each review question from the relevant search results by reviewing titles and abstracts – full papers were then obtained.
- Reviewed full papers against pre-specified inclusion / exclusion criteria to identify studies that addressed the review question in the appropriate population and reported on outcomes of interest (see review protocols in Appendix C).
- Critically appraised relevant studies using the appropriate checklist as specified in The Guidelines Manual.[77]
- Extracted key information about the study's methods and results into evidence tables (see evidence tables are included in Appendix E).
- Generated summaries of the evidence by outcome (included in the relevant chapter write-ups):
  - Randomised studies: meta analysed, where appropriate and reported in GRADE profiles (for clinical studies) – see below for details
  - Observational studies: data presented as a range of values in GRADE profiles
  - Qualitative studies: each study summarised in a table where possible, otherwise presented in a narrative.

3.3.1 Inclusion/exclusion

Evidence was searched and assessed according to the review protocols for each clinical question formed. See the review protocols in Appendix C for full details.

A major consideration in determining the inclusion and exclusion criteria in the protocol was the applicability of the evidence to the guideline population. The population within the scope of the guideline is hospitalised adults, with the exclusion of certain populations from the scope and this is broadly adhered to in most reviews. However, the GDG discussed and decided upon additional inclusion or exclusion criteria for each protocol according to the clinical context of the review question. In areas where evidence was anticipated to be lacking, decisions were made to consider populations or settings not included within this guideline if the GDG considered the evidence as indirectly applicable. Some examples of how this was applied include:

- patients who had major cardiac surgery were excluded in IV fluid intervention reviews on types and volumes of fluid, but included in the assessment of weight monitoring
- studies of resuscitation conducted in the ICU setting were included in the resuscitation review
- The search for evidence for fluid replacement included patients with diabetes mellitus.

More information about "Indirectness", is available in 3.3.7

Laboratory studies were excluded because the populations used (healthy volunteers, animals or *in vitro*) and settings are artificial and not comparable to the population we are making

recommendations for. These studies would undoubtedly be of very low quality as assessed by GRADE and therefore RCTs, cohort studies or GDG consensus opinion was considered preferable.

Literature reviews, letters and editorials, foreign language publications and unpublished studies were excluded.

3.3.2 Methods of combining clinical studies

Data synthesis for intervention reviews

Where possible, meta-analyses were conducted to combine the results of studies for each review question using Cochrane Review Manager (RevMan5) software. Fixed-effects (Mantel-Haenszel) techniques were used to calculate risk ratios (relative risk) for the binary outcomes. The continuous outcomes were analysed using an inverse variance method for pooling weighted mean differences and where the studies had different scales, standardised mean differences were used.

Statistical heterogeneity was assessed by considering the chi-squared test for significance at $p < 0.1$ or an I-squared inconsistency statistic of >50% to indicate significant heterogeneity. Where there was heterogeneity and a sufficient number of studies, sensitivity analyses were conducted based on risk of bias and pre-specified subgroup analyses were carried out as defined in the protocol. Assessments of potential differences in effect between subgroups were based on the chi-squared tests for heterogeneity statistics between subgroups. If no sensitivity analysis was found to completely resolve statistical heterogeneity then a random effects (DerSimonian and Laird) model was employed to provide a more conservative estimate of the effect.

The means and standard deviations of continuous outcomes were required for meta-analysis. However, in cases where standard deviations were not reported, the standard error was calculated if the p-values or 95% confidence intervals were reported and meta-analysis was undertaken with the mean difference and standard error using the generic inverse variance method in Cochrane Review Manager (RevMan5) software. Where p values were reported as “less than”, a conservative approach was undertaken. For example, if p value was reported as “$p < 0.001$”, the calculations for standard deviations were based on a p value of 0.001. If these statistical measures were not available then the methods described in section 16.1.3 of the Cochrane Handbook 121 ‘Missing standard deviations’ were applied as the last resort.

For binary outcomes, absolute differences in event rates were also calculated using the GRADEpro software using total event rate in the control arm of the pooled results and presented in the “Clinical Summary of Findings Table”.

Pre-specified subgroup analyses were conducted for populations of interest. These are groups were it had been identified that the interventions were likely to have different effect (effect modifiers), rather than prognostic factors. Although prognostic factors are usually not good candidates for subgrouping in meta-analysis, it is often impossible to completely predict whether a potential difference in effect is due to a difference in how the intervention may work in a group, or in how it will affect all outcomes; for example active cancer is a prognostic factor, but can also possibly affect how anticoagulants work. When such subgroups are identified, studies were sub grouped to observe whether there might be differences in effects between different groups of patients.

3.3.3 Appraising the quality of evidence by outcomes

The evidence for outcomes from the included RCT and observational studies were evaluated and presented using an adaptation of the ‘Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox’ developed by the international GRADE working group (http://www.gradeworkinggroup.org/). The software (GRADEpro) developed by the GRADE working

group was used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results. The "Clinical evidence profile" tables presented summarise the quality of evidence and the findings of the reviews in the guideline. The tables present the pooled outcome data (where appropriate), an absolute measure of intervention effect and the summary of quality of evidence for that outcome. In these tables, the columns for intervention and control indicate the sum of the sample size for continuous outcomes. For binary outcomes such as number of patients with an adverse event, the event rates (n/N: number of patients with events divided by sum of number of patients) are shown with percentages. Reporting or publication bias was only taken into consideration in the quality assessment and included in the Clinical Study Characteristics table if it was apparent.

Each outcome was examined separately for the quality elements listed and defined in **Table 2** and each graded using the quality levels listed in **Table 3**.The main criteria considered in the rating of these elements are discussed below (see section 3.3.4 Grading of Evidence). Footnotes were used to describe reasons for downgrading a quality element as having serious or very serious problems. The ratings for each component were summed to obtain an overall assessment for each outcome.

Table 2: Description of quality elements in GRADE for intervention studies

Quality element	Description
Limitations	Limitations in the study design and implementation may bias the estimates of the treatment effect. Major limitations in studies decrease the confidence in the estimate of the effect.
Inconsistency	Inconsistency refers to an unexplained heterogeneity of results.
Indirectness	Indirectness refers to differences in study population, intervention, comparator and outcomes between the available evidence and the review question, or recommendation made.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect relative to the clinically important threshold.
Publication bias	Publication bias is a systematic underestimate or an overestimate of the underlying beneficial or harmful effect due to the selective publication of studies.

Table 3: Levels of quality elements in GRADE

Level	Description
None	There are no serious issues with the evidence
Serious	The issues are serious enough to downgrade the outcome evidence by one level
Very serious	The issues are serious enough to downgrade the outcome evidence by two levels

Table 4: Overall quality of outcome evidence in GRADE

Level	Description
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

3.3.4 Grading the quality of clinical evidence

After results were pooled, the overall quality of evidence for each outcome was considered. The following procedure was adopted when using GRADE:

1. A quality rating was assigned, based on the study design. RCTs start HIGH and observational studies as LOW, uncontrolled case series as LOW or VERY LOW.

2. The rating was then downgraded for the specified criteria: Study limitations, inconsistency, indirectness, imprecision and reporting bias. These criteria are detailed below. Observational studies were upgraded if there was: a large magnitude of effect, dose-response gradient, and if all plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results showed no effect. Each quality element considered to have “serious” or “very serious” risk of bias was rated down -1 or -2 points respectively.

3. The downgraded/upgraded marks were then summed and the overall quality rating was revised. For example, all RCTs started as HIGH and the overall quality became MODERATE, LOW or VERY LOW if 1, 2 or 3 points were deducted respectively.

4. The reasons or criteria used for downgrading were specified in the footnotes.

The details of criteria used for each of the main quality element are discussed further in the following sections 3.3.5 to 3.3.8 .

3.3.5 Study limitations

The main limitations for randomised controlled trials are listed in **Table 5**

The decision of downgrading depends on whether methodological limitations resulted in potentially important risks of bias for an outcome. For example, it is well accepted that investigator blinding and/or participant blinding was impossible to achieve in some interventions (e.g. patient education or monitoring). Nevertheless, open-label studies would still be downgraded if there is an important risk of bias (for example if the outcome was subjective, or if other factors can affect the performance of the interventions). This is important to maintain a consistent approach in quality rating across the guideline. **Table 5** listed the limitations considered for randomised controlled trials and **Table 6** lists the important limitations considered for observational studies.

Table 5: Study limitations of randomised controlled trials

Limitation	Explanation
Allocation concealment	Those enrolling patients are aware of the group to which the next enrolled patient will be allocated (major problem in “pseudo” or “quasi” randomised trials with allocation by day of week, birth date, chart number, etc.)
Lack of blinding	Patient, caregivers, those recording outcomes, those adjudicating outcomes, or data analysts are aware of the arm to which patients are allocated
Incomplete accounting of patients and outcome events	Loss to follow-up not accounted and failure to adhere to the intention to treat principle when indicated
Selective outcome reporting	Reporting of some outcomes and not others on the basis of the results
Other limitations	For example: • Stopping early for benefit observed in randomised trials, in particular in the absence of adequate stopping rules • Use of unvalidated patient-reported outcomes • Carry-over effects in cross-over trials

Limitation	Explanation
	• Recruitment bias in cluster randomised trials

Table 6: Study limitations of cohort /observational studies

Limitation	Explanation
Failure to develop and apply appropriate eligibility criteria (inclusion of control population)	• under- or over-matching in case-control studies • selection of exposed and unexposed in cohort studies from different populations
Flawed measurement of both exposure and outcome	• differences in measurement of exposure (e.g. recall bias in case- control studies) • differential surveillance for outcome in exposed and unexposed in cohort studies
Failure to adequately control confounding	• failure of accurate measurement of all known prognostic factors • failure to match for prognostic factors and/or adjustment in statistical analysis

3.3.6 Inconsistency

Inconsistency refers to an unexplained heterogeneity of results. When estimates of the treatment effect across studies differ widely (i.e. heterogeneity or variability in results), this suggests true differences in underlying treatment effect. When heterogeneity exists (Chi square $p<0.1$ or I- squared inconsistency statistic of >50%), but no plausible explanation can be found, the quality of evidence was downgraded by one or two levels, depending on the extent of uncertainty to the results contributed by the inconsistency in the results. In addition to the I- square and Chi square values, the decision for downgrading was also dependent on factors such as whether the intervention is associated with benefit in all other outcomes or whether the uncertainty about the magnitude of benefit (or harm) of the outcome showing heterogeneity would influence the overall judgment about net benefit or harm (across all outcomes).

If inconsistency could be explained based on pre-specified subgroup analysis, the GDG took this into account and considered whether to make separate recommendations based on the identified explanatory factors, i.e. population and intervention. Where subgroup analysis gave a plausible explanation of heterogeneity, the quality of evidence was not downgraded.

3.3.7 Indirectness

Directness refers to the extent to which the populations, intervention, comparisons and outcome measures are similar to those defined in the inclusion criteria for the reviews. Indirectness is important when these differences are expected to contribute to a difference in effect size, or may affect the balance of harms and benefits considered for an intervention.

In this guideline, indirect evidence was an important source of information due to the breadth of population and the lack of evidence. Evidence for the target guideline population was often not available and indirect evidence was applied and interpreted based on the clinical expertise and experience of GDG members.

Examples of this include:

- indirect population: evidence from patients in critical care units for reviews on fluid resuscitation

- indirect outcome: pH values were used as surrogate outcomes for metabolic acidosis in the review on measurement of serum chloride.

Whenever indirect evidence was identified and applied, the evidence was downgraded for indirectness in GRADE and also discussed in the sections linking evidence to recommendation in the guideline.

3.3.8 Imprecision

Imprecision refers to the certainty in the effect for the outcome. When results are imprecise or very imprecise we are uncertain if there is an important difference between interventions or not.

The sample size, event rates and the resulting width of confidence intervals were the main criteria considered for evaluating imprecision.

The thresholds of important benefits or harms, or the minimally important differences (MID) for an outcome are important considerations for determining whether there is a "clinically important" difference between intervention and control groups and in assessing imprecision. For continuous outcomes, the MID is defined as "the smallest difference in score in the outcome of interest that informed patients or informed proxies perceive as important, either beneficial or harmful, and that would lead the patient or clinician to consider a change in the management" [36,42,98,99]. An effect estimate larger than the MID is considered to be "clinically important". For dichotomous outcomes, the MID is considered in terms of changes in both relative and absolute risk.

The GDG were asked at the outset of the guideline if they were aware of any established values for MID, for between group differences, for the outcomes included in the review. There were no published MIDs for any of the outcomes. The GDG agreed that the default values stated in the GRADEpro were appropriate for the outcomes. The default thresholds suggested by GRADE are a relative risk reduction of 25% (relative risk of 0.75 for negative outcomes) or a relative risk increase of 25% (risk ratio 1.25 for positive outcomes) for dichotomous outcomes. For continuous outcomes two approaches were used. When only one trial was included as the evidence base for an outcome, the mean difference was converted to the standardized mean difference (SMD) and checked to see if the confidence interval crossed 0.5. However, the mean difference (95% confidence interval) was still presented in the Grade tables. If two or more included trials reported a quantitative outcome then the default approach of multiplying 0.5 by standard deviation (taken as the median of the standard deviations across the meta-analyzed studies) was employed.

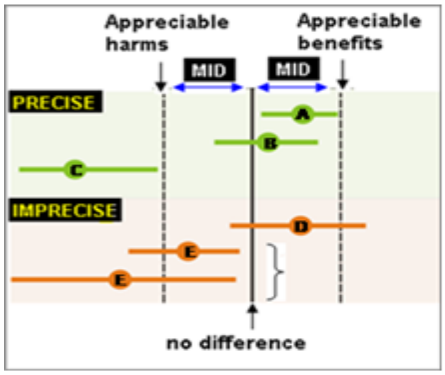
Assessing clinical importance and imprecision

The confidence interval for the pooled or best estimate of effect was considered in relation to the MIDs to assess imprecision. If the confidence interval crossed the MID threshold, there was uncertainty in the effect estimate supporting our recommendation (because the CI was consistent with two decisions) and the effect estimate was rated as having serious imprecision. If both MIDs were crossed, the effect estimate was rated as having very serious imprecision.

For the purposes of this guideline, clinical importance was assessed by comparing the effect estimate against the MID and reviewing the absolute effect reported in the GRADE summary table. For example, if the effect size was small (less than the MID), this finding suggests that there may not be enough difference to recommend one intervention over the other based on that outcome, unless in exceptional circumstances, the GDG agreed that the absolute effect was great enough to reach clinical importance. An effect estimate larger than the MID is considered to be clinically important. However, the GDG agreed that assessment of clinical importance when evaluating mortality would have to be interpreted taking into account the absolute increase in risk of mortality.

Figure 1 illustrates how the clinical importance of effect estimates were considered along with imprecision. This is documented in the evidence statements throughout this guideline.

Figure 1: Illustration of precise and imprecision outcomes based on the confidence interval of outcomes in a forest plot



Position of confidence interval	Evidence statement
A	Statistically significant but not clinically important
B	It is unlikely that there is any difference
C	Statistically significant and clinically important
D	Uncertain whether there is any difference
E	Statistically significant difference of uncertain clinical importance

Source: Figure adapted from GRADEPro software.

MID = minimal important difference determined for each outcome. The MIDs are the threshold for appreciable benefits and harms. The confidence intervals of the top three points of the diagram were considered precise because the upper and lower limits did not cross the MID. Conversely, the bottom three points of the diagram were considered imprecise because all of them crossed the MID and reduced our certainty of the results.

The confidence interval for the pooled or best estimate of effect was considered in relation to the MID, as illustrated in Figure 1. Essentially, if the confidence interval crossed the MID threshold, there was uncertainty in the effect estimate in supporting our recommendations (because the CI was consistent with two decisions) and the effect estimate was rated as imprecise.

For the purposes of this guideline, an intervention is considered to have a clinically important effect with certainty if the whole of the 95% confidence interval describes an effect of greater magnitude than the MID.

For mortality, the GDG agreed to consider any reduction in mortality as a clinically important difference for patients.

Evidence statements

Evidence statements were formed for each outcome indicating the quantity and quality of evidence available, and the outcome and population to which they relate. Where possible these were drafted for each subgroup or by outcome. An overall evidence summary for a particular intervention was presented, where possible.

3.4 Evidence of cost-effectiveness

The GDG is required to make decisions based on the best available evidence of both clinical and cost effectiveness. Guideline recommendations should be based on the expected costs of the different options in relation to their expected health benefits (that is, their 'cost effectiveness') rather than the total implementation cost. [76] Thus, if the evidence suggests that a strategy provides significant health benefits at an acceptable cost per patient treated, it should be recommended even if it would be expensive to implement across the whole population.

Evidence on cost-effectiveness related to the key clinical issues being addressed in the guideline was sought. The health economist undertook:

- A systematic review of the published economic literature.
- New cost-effectiveness analysis in priority areas.

3.4.1 Literature review

The health economist:

- Identified potentially relevant studies for each review question from the economic search results by reviewing titles and abstracts – full papers were then obtained.
- Reviewed full papers against pre-specified inclusion / exclusion criteria to identify relevant studies (see below for details).
- Critically appraised relevant studies using the economic evaluations checklist as specified in The Guidelines Manual.[76]
- Extracted key information about the studies' methods and results into evidence tables (included in Appendix F)
- Generated summaries of the evidence in NICE economic evidence profiles (included in the relevant chapter write-ups) – see below for details.

3.4.1.1 Inclusion/exclusion

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost–utility, cost-effectiveness, cost-benefit and cost-consequence analyses) and comparative costing studies that addressed the review question in the relevant population were considered potentially includable as economic evidence.

Studies that only reported cost per hospital (not per patient), or only reported average cost effectiveness without disaggregated costs and effects, were excluded. Abstracts, posters, reviews, letters/editorials, foreign language publications and unpublished studies were excluded. Studies judged to have an applicability rating of 'not applicable' were excluded (this included studies that took the perspective of a non-OECD country).

Remaining studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly applicable UK analysis was available other less relevant studies may not have been included. Where exclusions occurred on this basis, this is noted in the relevant section.

For more details about the assessment of applicability and methodological quality see the economic evaluation checklist (The Guidelines Manual), [76] and the health economics research protocol in Appendix C.7.

3.4.1.2 NICE economic evidence profiles

The NICE economic evidence profile has been used to summarise cost and cost-effectiveness estimates. The economic evidence profile shows, for each economic study, an assessment of applicability and methodological quality, with footnotes indicating the reasons for the assessment. These assessments were made by the health economist using the economic evaluation checklist from The Guidelines Manual.[76]. It also shows incremental costs, incremental effects (for example, quality-adjusted life years [QALYs]) and the incremental cost-effectiveness ratio, as well as information about the assessment of uncertainty in the analysis. See **Table 7** for more details.

If a non-UK study was included in the profile, the results were converted into pounds sterling using the appropriate purchasing power parity.[80]

Table 7: Content of NICE economic profile

Item	Description
Study	First author name, reference, date of study publication and country perspective.
Applicability	An assessment of applicability of the study to the clinical guideline, the current NHS situation and NICE decision-making*: • Directly applicable – the applicability criteria are met, or one or more criteria are not met but this is not likely to change the conclusions about cost effectiveness. • Partially applicable – one or more of the applicability criteria are not met, and this might possibly change the conclusions about cost effectiveness. • Not applicable – one or more of the applicability criteria are not met, and this is likely to change the conclusions about cost effectiveness.
Limitations	An assessment of methodological quality of the study*: • Minor limitations – the study meets all quality criteria, or the study fails to meet one or more quality criteria, but this is unlikely to change the conclusions about cost effectiveness. • Potentially serious limitations – the study fails to meet one or more quality criteria, and this could change the conclusion about cost effectiveness • Very serious limitations – the study fails to meet one or more quality criteria and this is very likely to change the conclusions about cost effectiveness. Studies with very serious limitations would usually be excluded from the economic profile table.
Other comments	Particular issues that should be considered when interpreting the study.
Incremental cost	The mean cost associated with one strategy minus the mean cost of a comparator strategy.
Incremental effects	The mean QALYs (or other selected measure of health outcome) associated with one strategy minus the mean QALYs of a comparator strategy.
Cost effectiveness	Incremental cost-effectiveness ratio (ICER): the incremental cost divided by the incremental effects.
Uncertainty	A summary of the extent of uncertainty about the ICER reflecting the results of deterministic or probabilistic sensitivity analyses, or stochastic analyses of trial data, as appropriate.

*Applicability and limitations were assessed using the economic evaluation checklist from The Guidelines Manual.[76]

3.4.2 Undertaking new health economic analysis

As well as reviewing the published economic literature for each review question, as described above, new economic analysis was undertaken by the health economist in selected areas. Priority areas for new health economic analysis were agreed by the GDG after formation of the review questions and consideration of the available health economic evidence.

The GDG identified monitoring, fluid type for resuscitation and fluid type for maintenance as the highest priority areas for original economic modelling (see sections 6.3.1.3, 6.3.2.3 7.2.3.3, 7.3.2, 7.2.4.2).

In all three areas, the systematic review did not produce strong enough evidence to evaluate cost-effectiveness, so cost analyses were developed. The following general principles were adhered to:

- Methods were consistent with the NICE reference case, where possible.[74].

- The GDG was involved in the design of the model, selection of inputs and interpretation of the results.
- •When published data was not available GDG expert opinion was used to populate the model.
- •Model inputs and assumptions were reported fully and transparently.
- •The results were subject to sensitivity analysis and limitations were discussed.
- •The model was peer-reviewed by another health economist at the NCGC.

Full methods for the cost analyses are described in Appendices L, M and N.

3.4.3 Cost-effectiveness criteria

NICE's report 'Social value judgements: principles for the development of NICE guidance' sets out the principles that GDGs should consider when judging whether an intervention offers good value for money.[75,76]In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

a. The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
b. The intervention cost less than £20,000 per QALY gained compared with the next best strategy.

If the GDG recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision are discussed explicitly in the 'from evidence to recommendations' section of the relevant chapter with reference to issues regarding the plausibility of the estimate or to the factors set out in the 'Social value judgements: principles for the development of NICE guidance'.[75] If a study reported the cost per life year gained but not QALYs, the cost per QALY gained was estimated by multiplying by an appropriate utility estimate to aid interpretation. The estimated cost per QALY gained is reported in the economic evidence profile with a footnote detailing the life-years gained and the utility value used. When QALYs or life years gained are not used in the analysis, results are difficult to interpret unless one strategy dominates the others with respect to every relevant health outcome and cost.

3.4.4 In the absence of economic evidence

When no relevant published studies were found, and a new analysis was not prioritised, the GDG made a qualitative judgement about cost effectiveness by considering expected differences in resource use between options and relevant UK NHS unit costs alongside the results of the clinical review of effectiveness evidence.

3.5 Developing recommendations

Over the course of the guideline development process, the GDG was presented with:

- Evidence tables of the clinical and economic evidence reviewed from the literature. All evidence tables are in Appendix E (clinical evidence) and Appendix F (economic evidence).
- Summary of clinical and economic evidence and quality (as presented in chapters 5-10.)
- Forest plots and summary ROC curves (Appendix G)
- A description of the methods and results of the cost-sensitivity analysis undertaken for the guideline (Appendices L, M, N)

Recommendations were drafted based on GDG interpretation of the available evidence, taking into account the balance of benefits and harms and evidence of cost effectiveness. When clinical and

economic evidence was of poor quality, conflicting or absent, the GDG drafted recommendations based on expert opinion. The considerations for making consensus based recommendations included the balance between potential harms and benefits, economic or implications compared to the benefits, current practices, recommendations made in other relevant guidelines, patient preferences and equality issues. Consensus on recommendations was achieved through discussions in the GDG meetings. The GDG also considered areas where the uncertainty was sufficient to justify delaying making a recommendation to await further research, taking into account the potential harm of failing to make a clear recommendation.

The main considerations specific to each recommendation are outlined in the Evidence to Recommendation Section preceding the recommendation section.

3.5.1 Research recommendations

When areas were identified for which good evidence was lacking, the guideline development group considered making recommendations for future research. Decisions about inclusion were based on factors such as:

- the importance to patients or the population
- national priorities
- potential impact on the NHS and future NICE guidance
- ethical and technical feasibility

For details of all research recommendations, see Appendix O.

3.5.2 Validation process

The guidance is subject to a six week public consultation and feedback as part of the quality assurance and peer review the document. All comments received from registered stakeholders are responded to in turn and posted on the NICE website when the pre-publication check of the full guideline occurs.

3.5.3 Updating the guideline

A formal review of the need to update a guideline is usually undertaken by NICE after its publication. NICE will conduct a review to determine whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an update.

3.5.4 Disclaimer

Health care providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by the practitioners in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

The National Clinical Guideline Centre disclaims any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines.

3.5.5 Funding

The National Clinical Guideline Centre was commissioned by the National Institute for Health and Care Excellence to undertake the work on this guideline.

4 Guideline summary

4.1 Key priorities for implementation

From the full set of recommendations, the GDG selected ten key priorities for implementation. The criteria used for selecting these recommendations are listed in detail in The Guidelines Manual.[77] The reasons that each of these recommendations was chosen are shown in the table linking the evidence to the recommendation in the relevant chapter. The recommendations are listed in the order they appear in the guideline.

Principles and protocol for intravenous fluid therapy

1. When prescribing IV fluids, remember the 5 Rs: Resuscitation, Routine maintenance, Replacement, Redistribution and Reassessment.
2. Offer IV fluid therapy as part of a protocol (see Algorithms for IV fluid therapy):

- Assess patients' fluid and electrolyte needs following Algorithm 1: Assessment.
- If patients need IV fluids for fluid resuscitation, follow Algorithm 2: Fluid resuscitation.
- If patients need IV fluids for routine maintenance, follow Algorithm 3: Routine maintenance.
- If patients need IV fluids to address existing deficits or excesses, ongoing abnormal losses or abnormal fluid distribution, follow Algorithm 4: Replacement and redistribution.

3. Patients should have an IV fluid management plan, which should include details of:

- the fluid and electrolyte prescription over the next 24 hours
- the assessment and monitoring plan.

Initially, the IV fluid management plan should be reviewed by an expert daily. IV fluid management plans for patients on longer-term IV fluid therapy whose condition is stable may be reviewed less frequently.

Assessment and monitoring

4. Assess the patient's likely fluid and electrolyte needs from their history, clinical examination, current medications, clinical monitoring and laboratory investigations:

- History should include any previous limited intake, thirst, the quantity and composition of abnormal losses (see Diagram of ongoing losses), and any comorbidities, including patients who are malnourished and at risk of refeeding syndrome (see Nutrition support in adults [NICE clinical guideline 32]).
- Clinical examination should include an assessment of the patient's fluid status, including:
  - pulse, blood pressure, capillary refill and jugular venous pressure
  - presence of pulmonary or peripheral oedema
  - presence of postural hypotension.
- Clinical monitoring should include current status and trends in:
  - National Early Warning Score (NEWS)
  - fluid balance charts
  - weight.
- Laboratory investigations should include current status and trends in:
  - full blood count
  - urea, creatinine and electrolytes.

5. All patients continuing to receive IV fluids need regular monitoring. This should initially include at least daily reassessments of clinical fluid status, laboratory values (urea, creatinine and electrolytes) and fluid balance charts, along with weight measurement twice weekly. Be aware that:

- Patients receiving IV fluid therapy to address replacement or redistribution problems may need more frequent monitoring.
- Additional monitoring of urinary sodium may be helpful in patients with high-volume gastrointestinal losses. (Reduced urinary sodium excretion [less than 30 mmol/l] may indicate total body sodium depletion even if plasma sodium levels are normal. Urinary sodium may also indicate the cause of hyponatraemia, and guide the achievement of a negative sodium balance in patients with oedema. However, urinary sodium values may be misleading in the presence of renal impairment or diuretic therapy.)
- Patients on longer-term IV fluid therapy whose condition is stable may be monitored less frequently, although decisions to reduce monitoring frequency should be detailed in their IV fluid management plan.

6. Clear incidents of fluid mismanagement (for example, unnecessarily prolonged dehydration or inadvertent fluid overload due to IV fluid therapy) should be reported through standard critical incident reporting to encourage improved training and practice (see Consequences of fluid mismanagement to be reported as critical incidents).

Resuscitation

7. If patients need IV fluid resuscitation, use crystalloids that contain sodium in the range 130–154 mmol/l, with a bolus of 500 ml over less than 15 minutes. (For more information see the Composition of commonly used crystalloids table.)

Routine maintenance

8. If patients need IV fluids for routine maintenance alone, restrict the initial prescription to:

- 25–30 ml/kg/day of water **and**
- approximately 1 mmol/kg/day of potassium[a], sodium and chloride **and**
- approximately 50–100 g/day of glucose to limit starvation ketosis. (This quantity will not address patients' nutritional needs; see Nutrition support in adults [NICE clinical guideline 32].)

For more information see IV fluid prescription (by body weight) for routine maintenance over a 24-hour period.

Training and education

9. Hospitals should establish systems to ensure that all healthcare professionals involved in prescribing and delivering IV fluid therapy are trained on the principles covered in this guideline, and are then formally assessed and reassessed at regular intervals to demonstrate competence in:

- understanding the physiology of fluid and electrolyte balance in patients with normal physiology and during illness
- assessing patients' fluid and electrolyte needs (the 5 Rs: Resuscitation, Routine maintenance, Replacement, Redistribution and Reassessment)
- assessing the risks, benefits and harms of IV fluids
- prescribing and administering IV fluids

[a] Weight-based potassium prescriptions should be rounded to the nearest common fluids available (for example, a 67 kg person should have fluids containing 20 mmol and 40 mmol of potassium in a 24-hour period). Potassium should not be added to intravenous fluid bags as this is dangerous.

- monitoring the patient response
- evaluating and documenting changes **and**
- taking appropriate action as required.

10. Hospitals should have an IV fluids lead, responsible for training, clinical governance, audit and review of IV fluid prescribing and patient outcomes.

4.2 Full list of recommendations

In this guideline, the term 'expert' refers to a healthcare professional who has core competencies to diagnose and manage acute illness. These competencies can be delivered by a variety of models at a local level, such as a critical care outreach team, a hospital-at-night team or a specialist trainee in an acute medical or surgical specialty. For more information, see Acutely ill patients in hospital (NICE clinical guideline 50).

Principles and protocols for intravenous fluid therapy:

The assessment and management of patients' fluid and electrolyte needs is fundamental to good patient care.

1. Assess and manage patients' fluid and electrolyte needs as part of every ward review. Provide intravenous (IV) fluid therapy only for patients whose needs cannot be met by oral or enteral routes, and stop as soon as possible.
2. Skilled and competent healthcare professionals should prescribe and administer IV fluids, and assess and monitor patients receiving IV fluids (see recommendations 26–28).
3. When prescribing IV fluids, remember the 5 Rs: Resuscitation, Routine maintenance, Replacement, Redistribution and Reassessment.
4. Offer IV fluid therapy as part of a protocol (see Algorithms for IV fluid therapy):

- Assess patients' fluid and electrolyte needs following Algorithm 1: Assessment.
- If patients need IV fluids for fluid resuscitation, follow Algorithm 2: Fluid resuscitation.
- If patients need IV fluids for routine maintenance, follow Algorithm 3: Routine maintenance.
- If patients need IV fluids to address existing deficits or excesses, ongoing abnormal losses or abnormal fluid distribution, follow Algorithm 4: Replacement and redistribution.

5. Include the following information in IV fluid prescriptions:

- The type of fluid to be administered.
- The rate and volume of fluid to be administered.

6. Patients should have an IV fluid management plan, which should include details of:

- the fluid and electrolyte prescription over the next 24 hours
- the assessment and monitoring plan.

Initially, the IV fluid management plan should be reviewed by an expert daily. IV fluid management plans for patients on longer-term IV fluid therapy whose condition is stable may be reviewed less frequently.

7. When prescribing IV fluids and electrolytes, take into account all other sources of fluid and electrolyte intake, including any oral or enteral intake, and intake from drugs, IV nutrition, blood and blood products.

8. Patients have a valuable contribution to make to their fluid balance. If a patient needs IV fluids, explain the decision, and discuss the signs and symptoms they need to look out for if their fluid balance needs adjusting. If possible or when asked, provide written information (for example, NICE's Information for the public), and involve the patient's family members or carers (as appropriate).

Assessment and monitoring:

Initial assessment

9. Assess whether the patient is hypovolaemic. Indicators that a patient may need urgent fluid resuscitation include:

- systolic blood pressure is less than 100 mmHg
- heart rate is more than 90 beats per minute
- capillary refill time is more than 2 seconds or peripheries are cold to touch
- respiratory rate is more than 20 breaths per minute
- National Early Warning Score (NEWS) is 5 or more
- passive leg raising suggests fluid responsiveness[b] .

10. Assess the patient's likely fluid and electrolyte needs from their history, clinical examination, current medications, clinical monitoring and laboratory investigations:

- History should include any previous limited intake, thirst, the quantity and composition of abnormal losses (see Diagram of ongoing losses), and any comorbidities, including patients who are malnourished and at risk of refeeding syndrome (see Nutrition support in adults [NICE clinical guideline 32]).
- Clinical examination should include an assessment of the patient's fluid status, including:
  - pulse, blood pressure, capillary refill and jugular venous pressure
  - presence of pulmonary or peripheral oedema
  - presence of postural hypotension.
- Clinical monitoring should include current status and trends in:
  - NEWS
  - fluid balance charts
  - weight.
- Laboratory investigations should include current status and trends in:
  - full blood count
  - urea, creatinine and electrolytes.

Reassessment

11. If patients are receiving IV fluids for resuscitation, reassess the patient using the ABCDE approach (Airway, Breathing, Circulation, Disability, Exposure), monitor their respiratory rate, pulse, blood pressure and perfusion continuously, and measure their venous lactate levels and/or arterial pH and base excess according to guidance on advanced life support (Resuscitation Council [UK], 2011)[90].

b Passive leg raising is a bedside method to assess fluid responsiveness in a patient. It is best undertaken with the patient initially semi-recumbent and then tilting the entire bed through 45°. Alternatively it can be done by lying the patient flat and passively raising their legs to greater than 45°. If, at 30–90 seconds, the patient shows signs of haemodynamic improvement, it indicates that volume replacement may be required. If the condition of the patient deteriorates, in particular breathlessness, it indicates that the patient may be fluid overloaded.

12. All patients continuing to receive IV fluids need regular monitoring. This should initially include at least daily reassessments of clinical fluid status, laboratory values (urea, creatinine and electrolytes) and fluid balance charts, along with weight measurement twice weekly. Be aware that:

- Patients receiving IV fluid therapy to address replacement or redistribution problems may need more frequent monitoring.
- Additional monitoring of urinary sodium may be helpful in patients with high-volume gastrointestinal losses. (Reduced urinary sodium excretion [less than 30 mmol/l] may indicate total body sodium depletion even if plasma sodium levels are normal. Urinary sodium may also indicate the cause of hyponatraemia, and guide the achievement of a negative sodium balance in patients with oedema. However, urinary sodium values may be misleading in the presence of renal impairment or diuretic therapy.)
- Patients on longer-term IV fluid therapy whose condition is stable may be monitored less frequently, although decisions to reduce monitoring frequency should be detailed in their IV fluid management plan.

13. If patients have received IV fluids containing chloride concentrations greater than 120 mmol/l (for example, sodium chloride 0.9%), monitor their serum chloride concentration daily. If patients develop hyperchloraemia or acidaemia, reassess their IV fluid prescription and assess their acid–base status. Consider less frequent monitoring for patients who are stable.

14. Clear incidents of fluid mismanagement (for example, unnecessarily prolonged dehydration or inadvertent fluid overload due to IV fluid therapy) should be reported through standard critical incident reporting to encourage improved training and practice (see Consequences of fluid mismanagement to be reported as critical incidents).

15. If patients are transferred to a different location, reassess their fluid status and IV fluid management plan on arrival in the new setting.

Resuscitation

16. If patients need IV fluid resuscitation, use crystalloids that contain sodium in the range 130–154 mmol/l, with a bolus of 500 ml over less than 15 minutes. (For more information, see the Composition of commonly used crystalloids table.)

17. Do not use tetrastarch for fluid resuscitation.

18. Consider human albumin solution 4–5% for fluid resuscitation only in patients with severe sepsis.

Routine maintenance

19. If patients need IV fluids for routine maintenance alone, restrict the initial prescription to:

- 25–30 ml/kg/day of water **and**
- approximately 1 mmol/kg/day of potassium[c], sodium and chloride **and**
- approximately 50–100 g/day of glucose to limit starvation ketosis. (This quantity will not address patients' nutritional needs; see Nutrition support in adults [NICE clinical guideline 32].)

For more information see the IV fluid prescription (by body weight) for routine maintenance over a 24-hour period.

[c] Weight-based potassium prescriptions should be rounded to the nearest common fluids available (for example, a 67 kg person should have fluids containing 20 mmol and 40 mmol of potassium in a 24-hour period). Potassium should not be added to intravenous fluid bags as this is dangerous.

20. For patients who are obese, adjust the IV fluid prescription to their ideal body weight. Use lower range volumes per kg (patients rarely need more than a total of 3 litres of fluid per day) and seek expert help if their BMI is more than 40 kg/m^2.

21. Consider prescribing less fluid (for example, 20–25 ml/kg/day fluid) for patients who:

- are older or frail
- have renal impairment or cardiac failure
- are malnourished and at risk of refeeding syndrome (see Nutrition support in adults [NICE clinical guideline 32]).

22. When prescribing for routine maintenance alone, consider using 25–30 ml/kg/day sodium chloride 0.18% in 4% glucose with 27 mmol/l potassium[d] on day 1 (there are other regimens to achieve this). Prescribing more than 2.5 litres per day increases the risk of hyponatraemia. These are initial prescriptions and further prescriptions should be guided by monitoring.

23. Consider delivering IV fluids for routine maintenance during daytime hours to promote sleep and wellbeing.

Replacement and redistribution

24. Adjust the IV prescription (add to or subtract from maintenance needs) to account for existing fluid and/or electrolyte deficits or excesses, ongoing losses (see Diagram of ongoing losses) or abnormal distribution.

25. Seek expert help if patients have a complex fluid and/or electrolyte redistribution issue or imbalance, or significant comorbidity, for example:

- gross oedema
- severe sepsis
- hyponatraemia or hypernatraemia
- renal, liver and/or cardiac impairment
- post-operative fluid retention and redistribution
- malnourished and refeeding issues (see Nutrition support in adults [NICE clinical guideline 32]).

Training and education

26. Hospitals should establish systems to ensure that all healthcare professionals involved in prescribing and delivering IV fluid therapy are trained on the principles covered in this guideline, and are then formally assessed and reassessed at regular intervals to demonstrate competence in:

- understanding the physiology of fluid and electrolyte balance in patients with normal physiology and during illness
- assessing patients' fluid and electrolyte needs (the 5 Rs: Resuscitation, Routine maintenance, Replacement, Redistribution and Reassessment)
- assessing the risks, benefits and harms of IV fluids
- prescribing and administering IV fluids
- monitoring the patient response

[d] Weight-based potassium prescriptions should be rounded to the nearest common fluids available (for example, a 67 kg person should have fluids containing 20 mmol and 40 mmol of potassium in a 24-hour period). Potassium should not be added to intravenous fluid bags as this is dangerous.

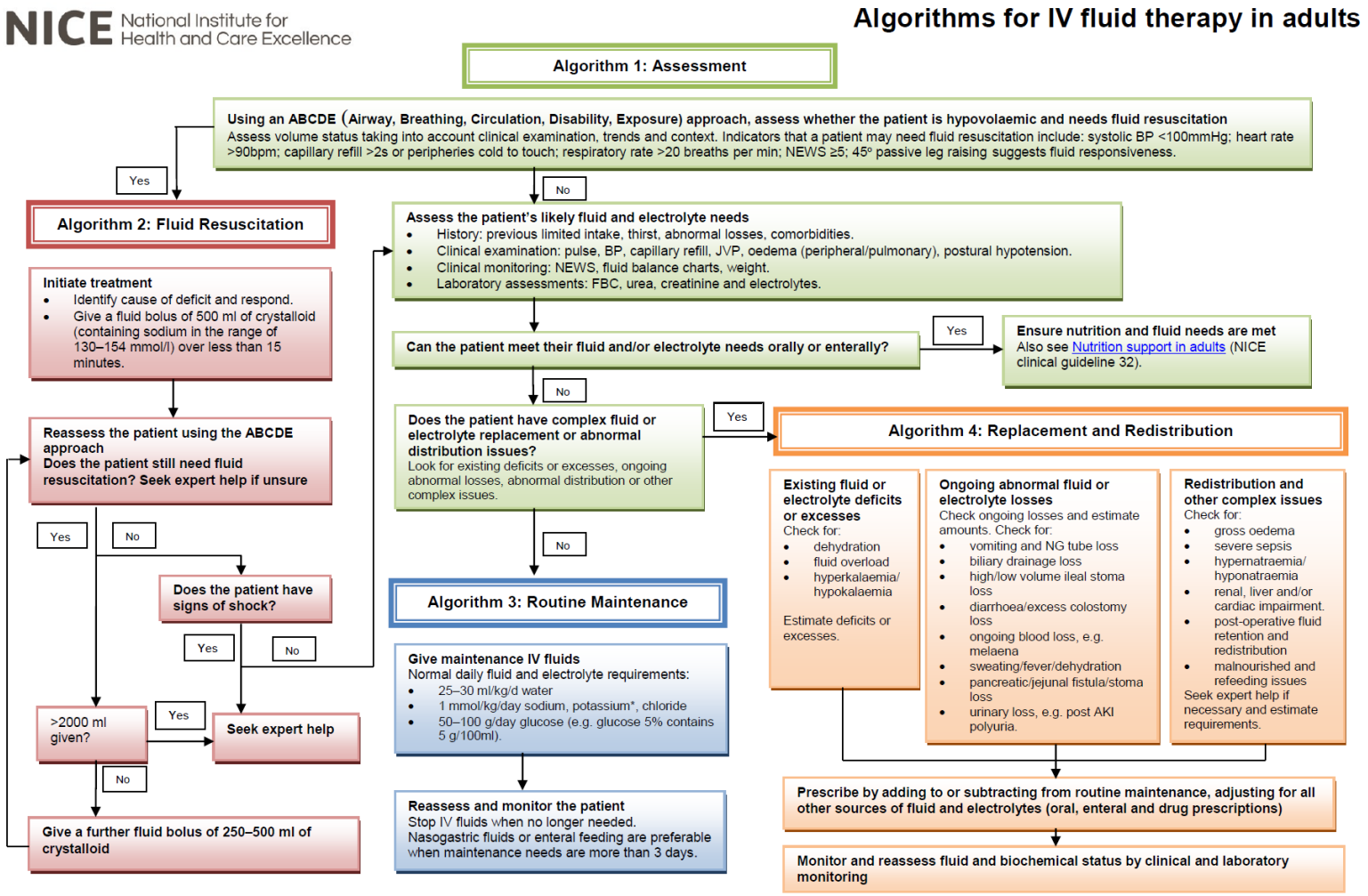
- evaluating and documenting changes **and**
- taking appropriate action as required.

27. Healthcare professionals should receive training and education about, and be competent in, recognising, assessing and preventing consequences of mismanaged IV fluid therapy, including:

- pulmonary oedema
- peripheral oedema
- volume depletion and shock.

28. Hospitals should have an IV fluids lead, responsible for training, clinical governance, audit and review of IV fluid prescribing and patient outcomes.

4.2.1 Algorithms for IV fluid therapy


NICE National Institute for Health and Care Excellence
Algorithms for IV fluid therapy in adults
Algorithm 1: Assessment
Using an ABCDE (Airway, Breathing, Circulation, Disability, Exposure) approach, assess whether the patient is hypovolaemic and needs fluid resuscitation
Assess volume status taking into account clinical examination, trends and context. Indicators that a patient may need fluid resuscitation include: systolic BP <100mmHg; heart rate >90bpm; capillary refill >2s or peripheries cold to touch; respiratory rate >20 breaths per min; NEWS ≥5; 45° passive leg raising suggests fluid responsiveness.
Yes
No
Algorithm 2: Fluid Resuscitation
Initiate treatment
Identify cause of deficit and respond.
Give a fluid bolus of 500 ml of crystalloid (containing sodium in the range of 130–154 mmol/l) over less than 15 minutes.
Reassess the patient using the ABCDE approach
Does the patient still need fluid resuscitation? Seek expert help if unsure
Yes
No
Does the patient have signs of shock?
Yes
No
>2000 ml given?
Yes
Seek expert help
No
Give a further fluid bolus of 250–500 ml of crystalloid
Assess the patient's likely fluid and electrolyte needs
History: previous limited intake, thirst, abnormal losses, comorbidities.
Clinical examination: pulse, BP, capillary refill, JVP, oedema (peripheral/pulmonary), postural hypotension.
Clinical monitoring: NEWS, fluid balance charts, weight.
Laboratory assessments: FBC, urea, creatinine and electrolytes.
Can the patient meet their fluid and/or electrolyte needs orally or enterally?
Yes
Ensure nutrition and fluid needs are met
Also see Nutrition support in adults (NICE clinical guideline 32).
No
Does the patient have complex fluid or electrolyte replacement or abnormal distribution issues?
Look for existing deficits or excesses, ongoing abnormal losses, abnormal distribution or other complex issues.
Yes
Algorithm 4: Replacement and Redistribution
No
Algorithm 3: Routine Maintenance
Give maintenance IV fluids
Normal daily fluid and electrolyte requirements:
25–30 ml/kg/d water
1 mmol/kg/day sodium, potassium*, chloride
50–100 g/day glucose (e.g. glucose 5% contains 5 g/100ml).
Reassess and monitor the patient
Stop IV fluids when no longer needed.
Nasogastric fluids or enteral feeding are preferable when maintenance needs are more than 3 days.
Existing fluid or electrolyte deficits or excesses
Check for:
dehydration
fluid overload
hyperkalaemia/ hypokalaemia
Estimate deficits or excesses.
Ongoing abnormal fluid or electrolyte losses
Check ongoing losses and estimate amounts. Check for:
vomiting and NG tube loss
biliary drainage loss
high/low volume ileal stoma loss
diarrhoea/excess colostomy loss
ongoing blood loss, e.g. melaena
sweating/fever/dehydration
pancreatic/jejunal fistula/stoma loss
urinary loss, e.g. post AKI polyuria.
Redistribution and other complex issues
Check for:
gross oedema
severe sepsis
hypernatraemia/ hyponatraemia
renal, liver and/or cardiac impairment.
post-operative fluid retention and redistribution
malnourished and refeeding issues
Seek expert help if necessary and estimate requirements.
Prescribe by adding to or subtracting from routine maintenance, adjusting for all other sources of fluid and electrolytes (oral, enteral and drug prescriptions)
Monitor and reassess fluid and biochemical status by clinical and laboratory monitoring

*Weight-based potassium prescriptions should be rounded to the nearest common fluids available (for example, a 67 kg person should have fluids containing 20 mmol and 40 mmol of potassium in a 24-hour period).
Potassium should not be added to intravenous fluid bags as this is dangerous.

'Intravenous fluid therapy in adults in hospital', NICE clinical guideline 174 (December 2013. Last update December 2016)

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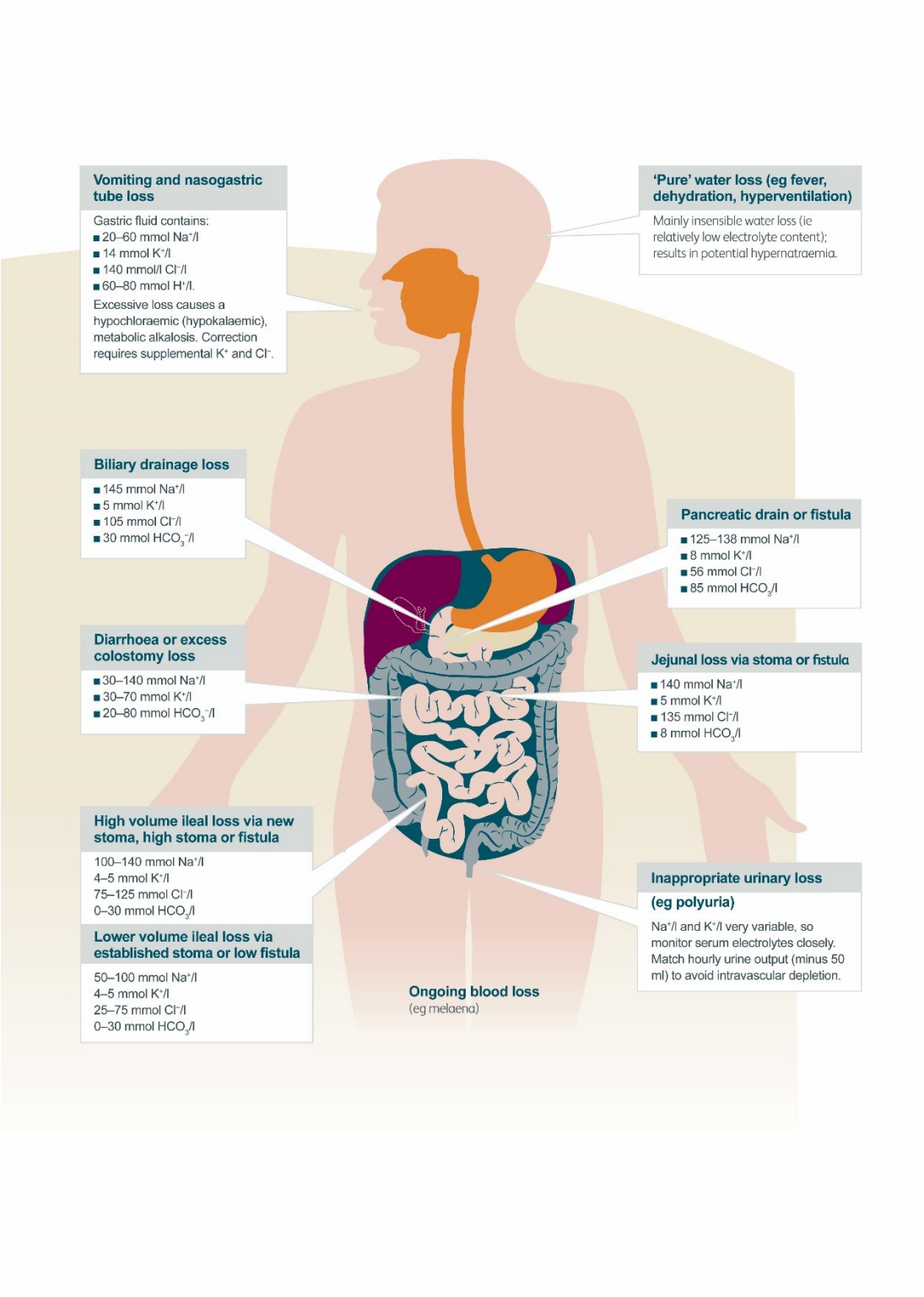
4.2.2 Diagram of ongoing losses


Vomiting and nasogastric tube loss
Gastric fluid contains:
20–60 mmol Na+/l
14 mmol K+/l
140 mmol/l Cl−/l
60–80 mmol H+/l.
Excessive loss causes a hypochloraemic (hypokalaemic), metabolic alkalosis. Correction requires supplemental K+ and Cl−.
'Pure' water loss (eg fever, dehydration, hyperventilation)
Mainly insensible water loss (ie relatively low electrolyte content); results in potential hypernatraemia.
Biliary drainage loss
145 mmol Na+/l
5 mmol K+/l
105 mmol Cl−/l
30 mmol HCO3−/l
Pancreatic drain or fistula
125–138 mmol Na+/l
8 mmol K+/l
56 mmol Cl−/l
85 mmol HCO3/l
Diarrhoea or excess colostomy loss
30–140 mmol Na+/l
30–70 mmol K+/l
20–80 mmol HCO3−/l
Jejunal loss via stoma or fistula
140 mmol Na+/l
5 mmol K+/l
135 mmol Cl−/l
8 mmol HCO3/l
High volume ileal loss via new stoma, high stoma or fistula
100–140 mmol Na+/l
4–5 mmol K+/l
75–125 mmol Cl−/l
0–30 mmol HCO3/l
Lower volume ileal loss via established stoma or low fistula
50–100 mmol Na+/l
4–5 mmol K+/l
25–75 mmol Cl−/l
0–30 mmol HCO3/l
Inappropriate urinary loss (eg polyuria)
Na+/l and K+/l very variable, so monitor serum electrolytes closely. Match hourly urine output (minus 50 ml) to avoid intravascular depletion.
Ongoing blood loss
(eg melaena)

Source: Copyright-National Clinical Guideline Centre

4.2.3 Consequences of fluid mismanagement to be reported as critical incidents

Consequence of fluid mismanagement	Identifying features	Time frame of identification
Hypovolaemia	Patient's fluid needs not met by oral, enteral or IV intake **and** • Features of dehydration on clinical examination • Low urine output or concentrated urine • Biochemical indicators, such as more than 50% increase in urea or creatinine with no other identifiable cause	Before and during IV fluid therapy
Pulmonary oedema (breathlessness during infusion)	• No other obvious cause identified (for example, pneumonia, pulmonary embolus or asthma) • Features of pulmonary oedema on clinical examination • Features of pulmonary oedema on X-ray	During IV fluid therapy or within 6 hours of stopping IV fluids
Hyponatraemia	• Serum sodium less than 130 mmol/l • No other likely cause of hyponatraemia identified	During IV fluid therapy or within 24 hours of stopping IV fluids
Hypernatraemia	• Serum sodium 155 mmol/l or more • Baseline sodium normal or low • IV fluid regimen included 0.9% sodium chloride • No other likely cause of hypernatraemia identified	During IV fluid therapy or within 24 hours of stopping IV fluids
Peripheral oedema	• Pitting oedema in extremities and/or lumbar sacral area • No other obvious cause identified (for example, nephrotic syndrome or known cardiac failure)	During IV fluid therapy or within 24 hours of stopping IV fluids
Hyperkalaemia	• Serum potassium more than 5.5 mmol/l • No other obvious cause identified	During IV fluid therapy or within 24 hours of stopping IV fluids
Hypokalaemia	• Serum potassium less than 3.0 mmol/l likely to be due to infusion of fluids without adequate potassium provision • No other obvious cause (for example, potassium-wasting diuretics, refeeding syndrome)	During IV fluid therapy or within 24 hours of stopping IV fluids

Weight-based potassium prescriptions should be rounded to the nearest common fluids available (for example, a 67 kg person should have fluids containing 20 mmol and 40 mmol of potassium in a 24-hour period). Potassium should not be added to intravenous fluid bags as this is dangerous.

4.2.4 IV fluid prescription (by body weight) for routine maintenance over a 24-hour period

Body weight	Water	Sodium, chloride, potassium		Body weight	Water	Sodium, chloride, potassium
kg	25–30 ml/kg/day	approx. 1 mmol/kg/day of each		kg	25–30ml/kg/day	approx. 1 mmol/kg/day of each
40	1000–1200	40		71	1775–2130	71
41	1025–1230	41		72	1800–2160	72
42	1050–1260	42		73	1825–2190	73
43	1075–1290	43		74	1850–2220	74
44	1100–1320	44		75	1875–2250	75

45	1125–1350	45		76	1900–2280	76
46	1150–1380	46		77	1925–2310	77
47	1175–1410	47		78	1950–2340	78
48	1200–1440	48		79	1975–2370	79
49	1225–1470	49		80	2000–2400	80
50	1250–1500	50		81	2025–2430	81
51	1275–1530	51		82	2050–2460	82
52	1300–1560	52		83	2075–2490	83
53	1325–1590	53		84	2100–2520	84
54	1350–1620	54		85	2125–2550	85
55	1375–1650	55		86	2150–2580	86
56	1400–1680	56		87	2175–2610	87
57	1425–1710	57		88	2200–2640	88
58	1450–1740	58		89	2225–2670	89
59	1475–1770	59		90	2250–2700	90
60	1500–1800	60		91	2275–2730	91
61	1525–1830	61		92	2300–2760	92
62	1550–1860	62		93	2325–2790	93
63	1575–1890	63		94	2350–2820	94
64	1600–1920	64		95	2375–2850	95
65	1625–1950	65		96	2400–2880	96
66	1650–1980	66		97	2425–2910	97
67	1675–2010	67		98	2450–2940	98
68	1700–2040	68		99	2475–2970	99
69	1725–2070	69		100	2500–3000	100
70	1750–2100	70		>100	2500–3000	100

1. Add 50-100 grams/day glucose (e.g. glucose 5% contains 5g/100ml).
2. For special considerations refer to the recommendations for routine maintenance.

Weight-based potassium prescriptions should be rounded to the nearest common fluids available (for example, a 67 kg person should have fluids containing 20 mmol and 40 mmol of potassium in a 24-hour period). Potassium should not be added to intravenous fluid bags as this is dangerous.

4.3 Key research recommendations

1. **What is the incidence of complications during, and as a consequence of, IV fluid therapy?**

2. **Are balanced solutions superior to sodium chloride 0.9% for the fluid resuscitation of patients with acute hypovolaemic shock?**

3. **Are balanced crystalloids superior to a combination of a balanced crystalloid and a gelatin suspended in a balanced solution for the fluid resuscitation of patients with acute hypovolaemic shock?**

4. **Does a higher sodium content IV fluid regimen for maintenance reduce the risk of developing hyponatraemia and volume depletion without increasing the risk of volume overload in hospitalised adults?**

5. **Does the introduction of hospital systems that ensure:**
   - **all hospital healthcare professionals involved in prescribing and delivering IV fluid therapy are appropriately trained in the principles of fluid prescribing; and**
   - **all IV fluid therapy-related complications are reported;**

   lead to a reduction in fluid-related complications and associated healthcare costs?

5 Principles and protocols for intravenous fluid therapy

Hospitalised patients need intravenous (IV) fluid and electrolytes for one or more of the following reason (the 4Rs):

Fluid resuscitation

IV fluids may need to be given urgently to restore circulation to vital organs following loss of intravascular volume due to bleeding, plasma loss, or excessive external fluid and electrolyte loss, usually from the gastrointestinal (GI) tract, or severe internal losses (e.g. from fluid redistribution in sepsis).

Routine maintenance

IV fluids are sometimes needed for patients who simply cannot meet their normal fluid or electrolyte needs by oral or enteral routes but who are otherwise well in terms of fluid and electrolyte balance and handling i.e. they are essentially euvolaemic, with no significant deficits, ongoing abnormal losses or redistribution issues. However, even when prescribing IV fluids for more complex cases, there is still a need to meet the patient's routine maintenance requirements, adjusting the maintenance prescription to account for the more complex fluid or electrolyte problems. Estimates of routine maintenance requirements are therefore essential for all patients on continuing IV fluid therapy.

Replacement

In some patients, IV fluids to treat losses from intravascular and or other fluid compartments, are not needed urgently for resuscitation, but are still required to correct existing water and/or electrolyte deficits or ongoing external losses. These losses are usually from the GI or urinary tract, although high insensible losses occur with fever, and burns patients can lose high volumes of what is effectively plasma. Sometimes, these deficits have developed slowly with associated compensatory adaptations of tissue electrolyte and fluid distribution that must be taken into account in subsequent replacement regimens (e.g. cautious, slow replacement to reduce risks of pontine demyelinosis).

Redistribution

In addition to external fluid and electrolyte losses, some hospital patients have marked internal fluid distribution changes or abnormal fluid handling. This type of problem is seen particularly in those who are septic, otherwise critically ill, post-major surgery or those with major cardiac, liver or renal co-morbidity. Many of these patients develop oedema from sodium and water excess and some sequester fluids in the GI tract or thoracic/peritoneal cavities.

Deciding on the optimal amount, composition and rate of administration of IV fluids to address these often complex needs is inherently difficult yet assessment, prescribing and monitoring of IV fluids in general admission and ward areas of hospitals, is often left to junior doctors and hard-pressed nurses who may lack required training and competence.[56,57,86,87,93]Evidence suggests that mismanagement of fluids is common, particularly in general ward areas with the potential for adverse outcomes including excess morbidity and mortality, prolonged hospital stays and increased costs.[6,39,73,105,116,117]

There is, therefore, a clear need for guidance on IV fluid prescribing applicable to general ward areas but since most randomized controlled trials of IV fluid therapy have examined narrow clinical questions in intensive care or intra-operative settings, many recommendations for more general use

must be based on first principles. All health professionals involved in prescribing and administering IV fluids need to understand these principles if they are to prescribe and manage IV fluid therapy safely and effectively.

5.1 The principles of fluid prescribing[e]

The knowledge needed to underpin safe and effective IV fluid and electrolyte prescribing lies in four areas:

- The physiology of fluid balance in health;
- Pathophysiological effects on fluid balance;
- Clinical approaches to assessing IV fluid needs;
- The properties of available IV fluids.

5.1.1 The physiology of fluid balance in health

When primitive marine unicellular organisms evolved into multicellular organisms and emerged onto land, they carried with them their own internal sea or extracellular fluid (ECF), in which their cells could bathe in a constant chemical environment. The French physiologist Claude Bernard called this the 'milieu interieur', [10] an environment in which the cells retain their energy consuming capacity to pump sodium out and retain potassium in order to neutralise the negative charges of proteins and other ions.

While fluid balance is usually considered as that between the body and its environment, i.e. external balance, disease also affects the internal balance between the various body fluid compartments, e.g. between the intravascular and interstitial components of the extracellular fluid compartment (ECF), between the intracellular fluid (ICF) and the ECF, and between the ECF and the gut and other internal spaces.[58,60] Appropriate IV fluid therapy depends on an understanding of the underlying physiology and pathophysiology and a consideration not only of external but internal fluid balance.[58]

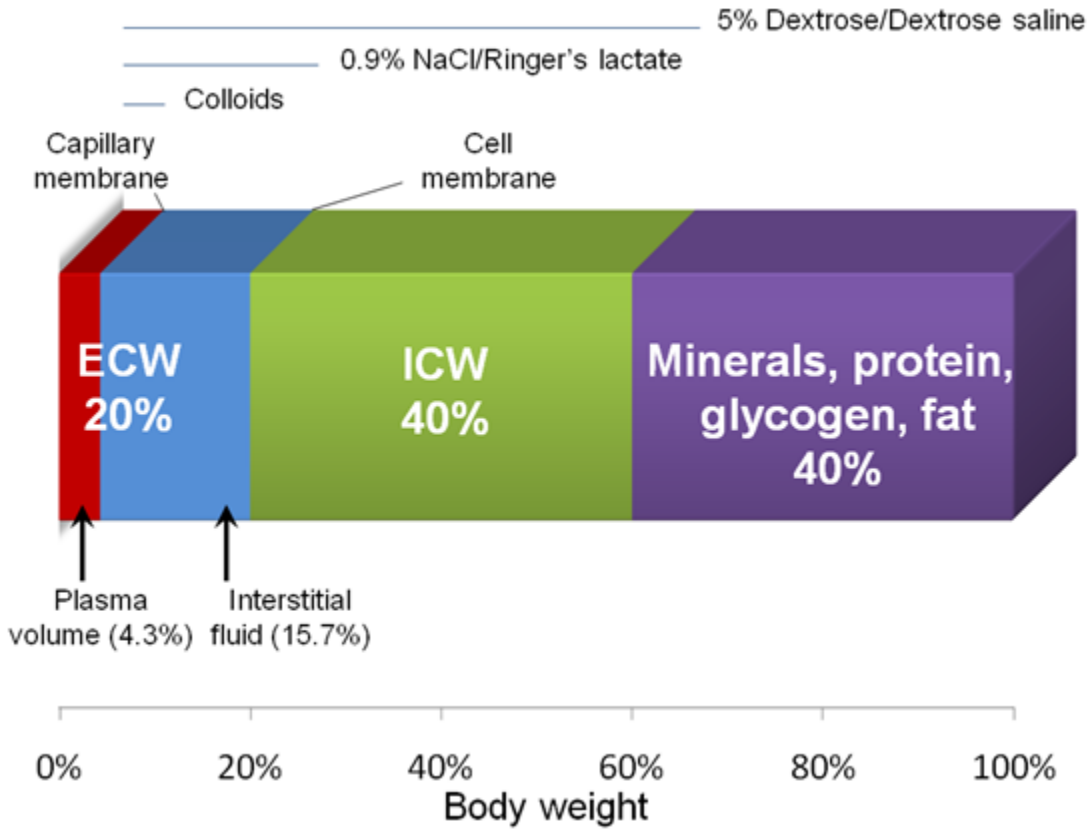
5.1.1.1 Normal anatomy and physiology

Water comprises approximately 60% of the body weight of an average adult (about 40L in a 70kg man).[29] The percentage is lower in obesity, since adipose tissue contains less water than lean tissue. It is also lower in women than in males because of the relatively greater amount of adipose tissue in women. The total body water is divided functionally into the extracellular (ECF=20% of body weight, about 14L in a 70kg man) and the intracellular fluid spaces (ICF= 40% of body weight, about 28L in a 70kg man) separated by the cell membrane with its active sodium pump, which ensures that sodium remains mainly in the ECF. The cell, however, contains large anions such as protein and glycogen, which cannot escape and, therefore, draw in K+ ions to maintain electrical neutrality (Gibbs-Donnan equilibrium). These mechanisms ensure that Na+ and its balancing anions, Cl- and HCO3-, are the mainstay of ECF osmolality, and K+ has the corresponding function in the ICF. The ECF is further divided into the intravascular (within the circulation) and the interstitial (extravascular fluid surrounding the cells) fluid spaces. The intravascular space (blood volume = 5-7% of body weight, approx. 4 – 5L) has its own intracellular component in the form of red (haematocrit = 40-45%) and white cells and an extracellular element in the form of plasma (55-60% of total blood volume). The normal distribution of fluids in the different body compartments is shown in Figure 2 which also shows the likely compartmental distribution of some different types of IV fluids (see section5.1.4).

[e] Some sections of the text in the introduction of this chapter are written by two GDG members who are also co-authors of a textbook on intravenous fluid therapy. The text book was commissioned by a pharmaceutical company (B.Braun) who own the copyright permissions. The company did not have any intellectual or editorial input into the text and the intellectual content of the text is the property of the GDG members. If the wording and sentiment of the text is similar, it can be attributed to the GDG members' direct involvement in both pieces of work.

The intravascular and extravascular components of the ECF are separated by the capillary membrane, with its micropores. The intravascular volume depends on plasma oncotic (colloid) pressure (POP) with plasma proteins retaining water in the circulation. POP is normally ~3.4kPa (26mmHg) with 75% of the effect due to albumin, 20% haemoglobin and 5% globulins. The plasma albumin concentration is ~35-52g/L, total body albumin is ~270g (120g intravascular, 150g ISF) and Figure 2(see below) illustrates the albumin cycle. A gram of albumin 'binds' ~18mls of water, thus normal plasma albumin concentrations bind ~2.25L (18mls x 120g) of intravascular 'plasma' water. Normally, the capillary micropores only allow a slow escape rate of albumin (5%/hr, 120g/day), which is then returned to the circulation via the lymphatics at the same rate, maintaining equilibrium.[30] While the hydrostatic pressure within the circulation drives fluid out, the oncotic pressure of the plasma proteins, e.g. albumin, draws fluid in. This maintains the relative constancy of the plasma volume as a proportion of the ECF (Starling effect). There is also a clinically important flux of fluid and electrolytes between the ECF and the GI tract involving active secretion and reabsorption of digestive juices. In health there is a constant flux between these various spaces and important physiological mechanisms ensure a constant relationship between them, which is termed the internal fluid balance.[58]

Figure 2: Body water compartments and approximate distribution of commonly used IV fluids



Source: Adapted from diagram(copyright obtained) by Dileep Lobo[58]

5.1.1.2 Fluid Balance

The external fluid and electrolyte balance between the body and its environment refers to the intake of fluid and electrolytes versus the output from kidneys, GI tract and the skin and lungs (insensible loss). The normal average daily intake and output of fluid and electrolytes are shown in Table 8 and Table 9 although these are very approximate and are modified greatly in the presence of excessive insensible losses e.g. of water and sodium in hot climates.

Table 8: Approximate daily water balance in health

Intake (ml)		Output (ml)	
Water from beverages	1200	Urine	1500
Water from solid food	1000	Insensible losses from skin and lungs	500 - 1000
Metabolic water from oxidation	300	Faeces	100

Table 9: Average daily intake [52]

Water	25-35 ml/kg/day
Sodium	Approx.1 mmol/kg/day
Potassium	Approx. 1 mmol/kg/day

5.1.1.3 Intake

Under normal circumstances most of our fluid intake is in the form of drinks but food also contains fluid and electrolytes, and water is also an end product of its oxidation which makes a further small but significant additional contribution to fluid intake. Drinking is governed by thirst, which is triggered when water balance is negative through insufficient intake or increased loss. It is also triggered by high sodium intake, since extra water is then needed to keep the ECF sodium concentration in the normal range.

Although, in the elderly, thirst may be blunted, in general it ensures that intake matches the bodily needs, maintaining zero balance and a steady physiological osmolality of 280-290mOsm/kg.

Claude Bernard coined the term 'volume obligatoire' to describe the minimum volume of urine needed to excrete waste products, e.g. urea, in order to prevent accumulation in the blood. This concept implies that, if sufficient fluid has been drunk or administered to balance insensible and other losses, and to meet the kidney's needs, there is no advantage in giving more. Indeed, excessive intakes of fluid and electrolytes may be hazardous under certain circumstances (see below) since they can overwhelm the kidneys' capacity to excrete the excess and maintain normal balance. Sodium and water excess in particular can cause oedema, although this only becomes an issue when the ECF has been expanded by at least 2-3 litres.[61]

5.1.1.4 Output

Insensible loss: evaporation of water from the lungs and skin occurs all the time without us being aware of it. In the UK climate, the amount lost is 0.5-1 litre/day but in hot climates, during fever or with exertion, losses of several litres of sweat can occur, containing up to 50 mmol/l of sodium.

Gastrointestinal losses: normally, the intestine absorbs water and electrolytes efficiently so that stool fluid loss is as little as 100-150 ml/day. However, in the presence of disease this may be greatly increased (see Section 5.1.2 and section on Intravenous fluid therapy for replacement and redistribution).

Kidneys: These are the main organs for fluid and electrolyte regulation and excretion of waste products from metabolism, e.g. urea. Their activity is controlled by pressure and osmotic sensors which result in changes in the secretion of hormones. The modest daily fluctuations in water and sodium intake cause small changes in plasma osmolality which trigger osmoreceptors. This in turn causes changes in thirst and the renal excretion of water and sodium. If blood or ECF volumes are subject to abnormal losses, volume receptors are triggered (see below) which override the

osmoreceptors. In the presence of large volume changes, therefore, the kidney is less able to adjust osmolality. This can be important in some clinical situations.

5.1.1.4.1 Water regulation:

Osmoreceptors which sense changes in plasma osmolality, are located in the hypothalamus and signal the pituitary to increase or decrease secretion of vasopressin or antidiuretic hormone (ADH). Dilution of the ECF, including plasma, by intake of water or fluid of lower osmolality than plasma, causes ADH secretion to fall, so that the kidneys excrete more free water and produce a dilute urine). Conversely, dehydration causes the ECF to become more concentrated, ADH secretion rises and the renal tubules reabsorb more water, producing concentrated urine. In response to dehydration, the normal kidney can concentrate urea in the urine up to a hundred-fold, so that the normal daily production of urea related to protein metabolism in health can be excreted in as little as 500 ml of urine.

In the presence of water deficit, the urine to plasma urea or osmolality ratio is, therefore, a measure of the kidney's concentrating capacity. Age and disease can impair the renal concentrating capacity so that a larger volume of urine is required in order to excrete the same amount of waste products. Also if protein catabolism increases due to a high protein intake or increased catabolism, a larger volume of urine is needed to clear the resulting increase in urea production.

To assess renal function, therefore, measurement of both urinary volume and concentration (osmolality) are important, and the underlying metabolic circumstances taken into account. If serum urea and creatinine concentrations are unchanged and normal, then, urinary output over the previous 24 hours has been sufficient, fluid intake has been adequate, and the urinary 'volume obligatoire' has been achieved.

5.1.1.4.2 Sodium (Na+) regulation:

Since the integrity of the ECF volume and its proportion of the total body water are largely dependent on the osmotic effect of Na+ and its accompanying anions, it is important that the kidneys maintain Na+ balance within narrow limits. If sodium depletion occurs, the ECF and plasma volumes fall. Pressure sensors in the circulation are then stimulated and these excite renin secretion by the kidney. This, in turn, stimulates aldosterone secretion by the adrenal gland, which acts on the renal tubules, causing them to reabsorb and conserve sodium.

Conversely, if the intake of Na+ is excessive, the renin-aldosterone system is supressed, allowing more Na+ to be excreted, until normal balance is restored. The mechanism for sodium conservation is extremely efficient and the kidney can reduce the concentration of Na+ in the urine to <5 mmol/l. On the other hand, even in health, we are slow to excrete an excess sodium load, possibly because human physiology evolved in the context of the hot, low sodium environment of Africa and has not until modern times been exposed to excessive sodium intake. The response of atrial natriuretic peptide to fluid infusions seems to be related more to volume (stretching of the right atrium) than sodium load per se.

The mechanism for maintaining sodium balance may be disturbed in disease, leading to Na+ deficiency or, more commonly, to excessive sodium retention, with consequent oedema and adverse clinical outcome.

5.1.1.4.3 Potassium (K+) regulation:

Although only a small proportion of the body's K+ is in the extracellular space, its concentration has to be maintained within narrow limits (3.5-5.3 mmol/l) to avoid the risk of muscular dysfunction or potentially fatal cardiac events. This is achieved by exchange of K+ in the renal tubules for Na+ or H+,

allowing more or less K+ to be excreted. In the presence of K+ deficiency, H+ ion reabsorption is impaired, leading to hypokalaemic alkalosis and a decrease in the kidneys' ability to excrete a sodium load.

5.1.2 Pathophysiological effects on fluid balance

Illness and injury alter fluid and electrolyte balance and distribution needs in many ways including:

- Non-specific metabolic responses to stress (especially in the seriously ill or injured);
- Changes in fluid or electrolyte handling directly attributable to specific organ or system dysfunction or the effects of drugs or other IV therapies used to treat such problems;
- Changes in fluid or electrolyte handling due to very restricted recent food intake or malnutrition.

5.1.2.1 Non-Specific responses to illness and injury

In the 1930's, Cuthbertson[22] described the metabolic changes, which occur in response to injury (including surgery and sepsis), as an increase in metabolic rate and protein breakdown to meet the requirements for healing. These changes were later shown to be due to neuroendocrine and cytokine changes and to occur in three phases. The ebb or shock phase is brief and is modified by resuscitation. This gives way to the flow or catabolic phase, the length and intensity of which depends on the severity of injury and its complications. As inflammation subsides, the convalescent anabolic phase of rehabilitation begins. In parallel with these metabolic changes, there are changes in water and electrolyte physiology. During the flow phase, there is an increase in ADH, cortisol and aldosterone secretion, especially if there has been any reduction in blood or ECF volume. These lead to retention of sodium and water with loss of potassium.[121,122] The normal, if somewhat sluggish, ability to excrete an excess of sodium and water load is then further diminished, leading to ECF expansion and oedema. [58]

These non-specific responses imply that a degree of oliguria is normal in the context of serious illness or injury, [110] and hence that the presence of oliguria does not necessarily indicate a need to increase administration of sodium and water or plasma expanders unless there are also indications of intravascular volume deficit, e.g. from postoperative bleeding. Indeed, sodium and water retention after injury can be seen as nature's way of trying to protect the ECF and circulating volume at all costs. It also explains why sick patients can be so easily overloaded with excessive IV sodium and water administration during the flow phase. Since water as well as sodium is retained, it is also easy to cause hyponatraemia by giving excess water or hypotonic fluid. It is important, therefore, to administer crystalloids, not only in the correct volume but also in the appropriate concentration especially as, in the presence of these responses to illness or injury, the kidneys are unable to correct for errors in prescribing, even in the absence of significant acute kidney injury (AKI) or other renal pathology.

The convalescent phase of serious illness or injury is not only characterised by the return of anabolism but also by a returning capacity to excrete any excess sodium and water load that has been accumulated. These periods have been termed the 'sodium retention phase' and the 'sodium diuresis phase' of injury.

Transcapillary escape rate of albumin

The responses to serious illness of injury also includes an increase in the size of the pores in the capillary membrane and the transcapillary escape rate of albumin increases by up to 300% from about 5%/h in health to 13-15%/h.[30] Subsequent falls in plasma albumin then reduce POP and intravascular volume, whilst increases in ISF albumin promote oedema. This phenomenon can last

from several hours to days. Albumin and other plasma proteins leak out from the intravascular compartment into the interstitial space and water and sodium also move into that space. This results in a net contraction of the intravascular compartment and expansion of the interstitial space. As the return of albumin to the circulation via the lymphatics is unchanged, the net result is an intravascular hypovolaemia with oedema .

Potassium

Potassium losses during serious illness and injury are not only secondary to increased excretion from high cortisol and aldosterone levels, but also to protein and glycogen catabolism. As intracellular protein is broken down and its constituent amino acids are released from cells, so intracellular negative charges are lost and K+, with its balancing positive charges, passes out into the ECF to be excreted. In situations where catabolism is extreme and renal function is impaired, the outflow of K+ from the cells may exceed the kidney's capacity to excrete it, causing dangerous hyperkalaemia. Conversely, in the convalescent phase, as net intracellular protein and glycogen anabolism is restored, the cells take up again and the patient's K+ intake has to be increased to prevent the development of hypokalaemia and to help with the excretion of a likely total excess in body sodium.

Malnutrition is common in hospital patients since it is both a cause and a consequence of illness and injury. When present, it can have non-specific effects on fluid and electrolyte status and handling since starvation is accompanied by reductions in cell membrane pumping, with consequent movement of more sodium and water into cells than usual, while simultaneously potassium, magnesium, calcium and phosphate move out of cells and are excreted by the kidneys. A malnourished individual therefore tends to have a degree of total body sodium and water overload, coupled with depletion of total body potassium, phosphate, magnesium and calcium. These changes are often unrecognized as plasma levels may remain normal. The most important problems caused by these changes in relation to IV fluid and electrolyte prescribing, occur when a malnourished individual is fed, even if that feeding is only in the form of glucose from IV infusions. The arrival of the glucose, coupled with the release of insulin it triggers, can reverse the depression of the membrane pumps, leading to cellular uptake of potassium, phosphate, magnesium and calcium with potentially dangerous falls in plasma levels.[104] At the same time, there is a net movement of sodium and water out of cells into the circulation, a redistribution change that is effectively added to any IV fluids being administered but is frequently unaccounted for. Since malnourished individuals may have diminished cardiac reserve and/or hidden infection with high capillary escape rates, the consequence of all the above may be potentially lethal fluid overload and cardiac instability. These problems are known as the refeeding syndrome and specific advice on the prevention and management of these problems is provided in the NICE guideline on Nutrition Support in adults.

5.1.2.2 Effects of specific organ or system dysfunction

Many specific medical conditions can alter the body's fluid and electrolyte handling, as can many of the therapies used to treat such problems. Detailed discussions of such changes are clearly not possible within this guidance but examples of issues that might influence IV fluid prescriptions are shown in Table 10. The organ or system dysfunction may be the either the primary problem that has brought the patient into hospital or a significant co-morbidity)

Table 10: Issues influencing IV fluid prescriptions

Organ/System	Considerations when prescribing IV fluids
Cardiac dysfunction	Increased vulnerability to fluid and sodium overload with consequent congestive failure. Potential for hypokalaemia from diuretics and renin/angiotensin/aldosterone activation, or hyperkalemia from potassium sparing diuretics. Severe cardiac patients may also have consequent renal or liver impairment.

Organ/System	Considerations when prescribing IV fluids
Renal disease	Impaired clearance or excessive losses of both fluids and electrolytes in both acute and chronic kidney disease. Disordered calcium and phosphate handling in chronic renal failure.
Gastrointestinal problems	High losses of both fluid and electrolytes are seen in many GI problems, and patients with ileus can sequester large volumes of electrolyte rich fluid.
Liver disease	Very abnormal fluid and electrolyte handling with a tendency for marked sodium and water retention due to complex pathophysiological changes including hyper-aldosteronism. Moderate to severe renal impairment is seen in many patients – the hepato-renal syndrome).
Respiratory disease	High respiratory fluid losses but many patients are vulnerable to fluid overload. SIADH common. Cor-pulmonale makes patients vulnerable to venous circulatory overload, sometimes with hepatic congestion and dysfunction.
Neurology	Hypothalamic or pituitary disease can severely damage fluid regulatory mechanisms. High concentration IV saline is sometime administered to try to reduce intracranial pressure.
Dermatology	Burns and other extensive skin inflammatory problems can lead to very high fluid/plasma loss.
Endocrine	Problems including diabetes mellitus, Addison's disease and SIADH can markedly alter fluid and electrolyte handling.

5.1.2.3 Effects due to very restricted recent food intake or malnutrition.

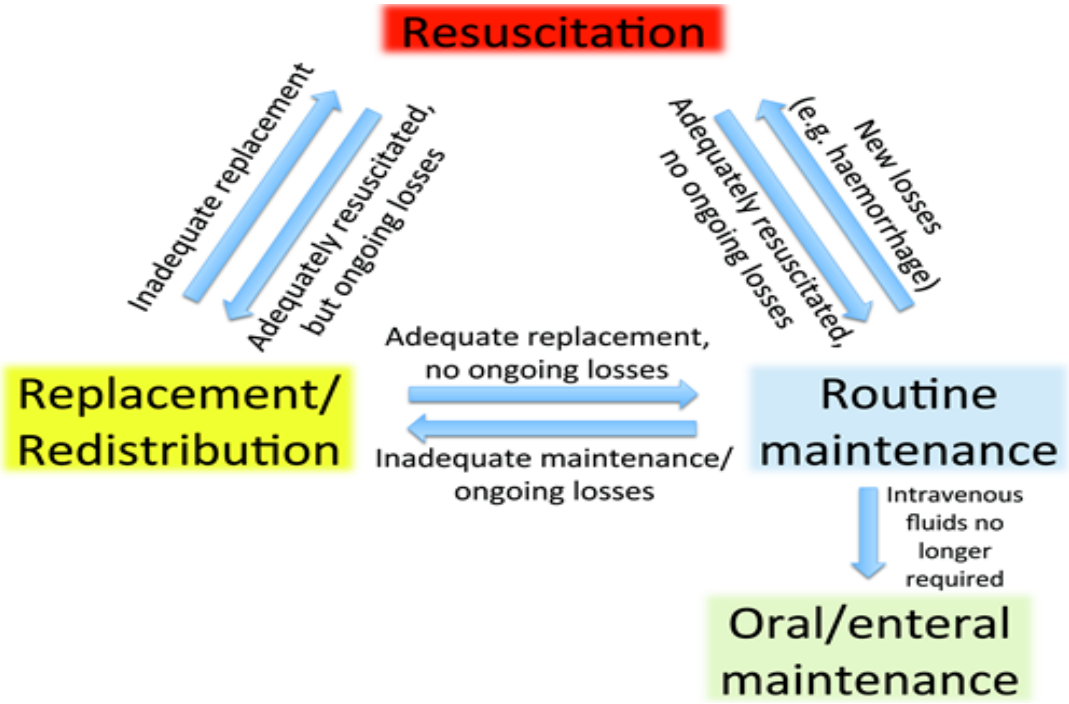
Some degree of starvation is common in individuals who are ill or injured, especially those who might need IV fluid therapy. Reduced or absent food intake leads quite swiftly to alterations in cell function which include a reduction in membrane pumping so that potassium leaks out of the cells and is then lost in the urine, while sodium and water move into cells. Malnourished individuals, and even those who are overweight but have a history of recent starvation, may therefore have lower than expected total body potassium and higher total salt and water content. This makes them potentially vulnerable to fluid mismanagement, especially since malnutrition can also cause a decrease in cardiac reserve, a decrease in renal capacity to clear salt and water, and deficiencies of specific vitamins. Furthermore. This vulnerability is further enhanced if significant feeding is introduced at the same time as IV fluids withy the potential for inducing low phosphate, potassium or magnesium as part of the refeeding syndrome (see Guidance of Refeeding syndrome in NICE CG32 – Nutrition Support in Adults).

5.1.3 The clinical approach to assessing IV fluid needs

The most appropriate method of fluid and electrolyte administration is the simplest, safest and effective. The oral route should be used whenever possible and IV fluids can usually be avoided in patients who are eating and drinking. The possibility of enteral tube administration should also be considered if safe oral intake is compromised but there is enteral tube-accessible GI function.

Figure 3 illustrates the '4 Rs' that underpin the clinical approach to deciding IV fluid needs: Resuscitation, Routine maintenance, Replacement and Redistribution. There is also a '5th R' for Reassessment.

Figure 3: The 4 Rs - Resuscitation, Routine maintenance, Replacement and Redistribution.[58] A 5th R – Reassessment is also a critical element of care.



Source: Adapted from diagram(copyright obtained) by Dileep Lobo[58]

Clinical considerations around the '4Rs' can be complex and so decisions on the optimal amount, composition and rate of IV fluid administration must be based on careful, individual patient assessment. However, the clinical principles underlying these decisions can be approached as a series of questions.

Does my patient need IV fluid resuscitation?

This is the first question, since urgent IV fluid therapy is a critical element in the management of most shocked patients. For details on prescribing for routine maintenance see section Intravenous fluid therapy for fluid resuscitation.

Can my patient meet fluid and electrolyte needs by the oral or enteral route?

The unnecessary use of IV fluids should be avoided. When they are needed, they should be stopped as soon as possible.

What is my patient's current fluid and electrolyte status?

Assessment must be informed by all information available including a focussed history and examination along with results of clinical monitoring (e.g. NEWS, fluid balance and body weight) and laboratory results. For details on assessment and monitoring, see section Assessment and monitoring of patients receiving intravenous fluid therapy.

What are my patient's routine maintenance needs for fluid and electrolytes?

The average person requires 25-30 ml/kg water per day and about 1 mmol/kg of Na+ and K+. For details on prescribing for routine maintenance see section Intravenous fluid therapy for routine maintenance.

Does my patient have existing fluid or electrolyte deficits or abnormal ongoing losses?

All IV fluid prescriptions should add enough fluid and/or electrolytes to correct any existing deficits or meet abnormal ongoing losses, to estimates of routine maintenance requirements. Recommendations and more details on fluid prescription for replacement are covered in the section Intravenous fluid therapy for replacement and redistribution.

Does my patient have problems with internal redistribution of fluid or other fluid handling issues from either their primary problem or significant co-morbidities?

IV fluid prescriptions must aim to account for both non-specific responses to illness or injury described in Section 5.1.2 as well as the more complex problems of fluid distribution or handling caused by specific organ or system dysfunction and/or malnutrition. Recommendations and more details on these issues are also covered in the section Intravenous fluid therapy for replacement and redistribution.

Consideration of all questions above allows estimates of the total volume of IV fluid and amounts of electrolytes that should be given, before deciding on the best rate at which to administer the fluids. Often, that rate needs to be slow in order not to overload the circulation or to cause acute electrolyte problems, since time is needed for transmembrane (i.e. ECF/ICF) physiological equilibrations to occur. The best IV fluid (or mix of fluids) to use can then be chosen although, before completing the prescription, allowance must be made for any fluid and electrolytes intake from other sources. These include any food and drinks, enteral tube provision and other IV therapies. Blood or blood products, in particular, contain large amounts of electrolytes as do some IV drugs, especially those given in larger volume diluents, several times a day. Patients on artificial parenteral or enteral nutrition usually receive adequate fluid and electrolytes from their feed to meet at least routine maintenance needs and prescription of unnecessary additional IV fluids in such patients is a common mistake.

5.1.4 The properties of available IV fluids

Many different crystalloids, artificial colloids and albumin solutions are available for IV fluid therapy. The aim is to meet estimates of total fluid and electrolyte requirements. There are theoretical advantages to giving a colloid instead of a crystalloid when resuscitating the hypovolaemic patient because colloid-based fluids generally remain for longer in the circulation. Crystalloids are distributed throughout the ECF and traditional teaching is that their infusion has relatively limited and transient effects on plasma volume. However, such considerations are based on data derived from studies undertaken in euvolaemic human volunteers who have no illness-induced abnormalities in fluid distribution and capillary permeability, and in hypovolaemic patients, crystalloids have much better intravascular retention than these studies have suggested. The actual benefits, if any, of colloids over crystalloids when intravascular volume expansion is required are therefore unclear.

A review of all the available IV fluids in the UK is beyond the remit of this guidance but understanding the composition and properties of some of those more commonly used provides much of the understanding needed to prescribe any fluid appropriately. Furthermore, it helps understanding of the issues in fluid prescribing which are of debate in current practice.

See Appendices P.1 and P.2 for details on the composition of commonly used crystalloids and colloids which have been reviewed as part of the evidence for this guideline. A brief description of some of the available fluids highlighting their properties and potential pros and cons of their usage is detailed below.

Isotonic saline

Sodium chloride 0.9% with or without additional potassium is one of the most commonly used IV fluids in UK practice. However, questions have been raised in relation to its appropriate use. As with all crystalloids, sodium chloride 0.9% is distributed throughout the ECF and infusion usually has a more transient effect on plasma volume than colloids. Traditionally sodium chloride 0.9% infusion has been considered to expand blood volume by only a quarter to a third of the volume infused, the remainder being sequestered in the interstitial space. [18,59,62,89] In practice, for the reasons given above, intravascular retention of sodium chloride 0.9% is likely to better than this in hypovolaemic and stressed patients. Theoretically, use of sodium chloride 0.9% for plasma volume expansion might cause more oedema than would occur with use of a colloid but such a difference is seldom realised in practice.

In addition, it is also possible that a significant albeit lesser degree of unnecessary sodium and water retention, is a problem when sodium chloride 0.9% is used for routine maintenance. The normal daily requirements of sodium are only 70-100mmol but one litre of normal saline contains 154mmol, so it is easy to give an excess. This will then need to be excreted but the ability to clear a solute load is limited even in health and may be further impaired during illness or injury.

Another issue that raises questions about the widespread usage of sodium chloride 0.9% is the fact that it produces a degree of hyperchloraemia due to its high chloride content compared with plasma. This in turn could lead to significant reductions in renal blood flow and glomerular filtration [18] as well as hyperchloraemic acidosis, gastrointestinal mucosal acidosis and ileus.[59]

Some GI fluid losses and occasionally renal losses are very high in sodium chloride and hence sodium chloride 0.9% use may well be appropriate in situations where there are ongoing high sodium losses or deficits of sodium, chloride and water from earlier losses. It is important to recognize, however, that many of these losses will be high in potassium, calcium and magnesium and so a balanced crystalloid might have advantages over sodium chloride 0.9% with added potassium.

Balanced crystalloid solutions

Balanced crystalloids are also distributed throughout the ECF and are therefore of similar efficacy to sodium chloride 0.9% in terms of plasma volume expansion. However, they do have theoretical advantages in that they contain somewhat less sodium and significantly less chloride, and they may already have some potassium, calcium and magnesium content. The use of balanced crystalloids could therefore have advantages over sodium chloride 0.9% when used for resuscitation or routine maintenance and preparations with more specialized ‘resuscitation’ and ‘maintenance’ versions, with content tailored to meet more closely the theoretical requirements for these different circumstances, are likely to become increasingly available in future. Balanced solutions containing lactate or other buffers might also grant advantages in situations of significant acidosis which is often seen when resuscitation is needed.

Glucose and glucose salines

Solutions such as 5% glucose and glucose/ saline with or without potassium are not meant for resuscitation or replacement of electrolyte rich losses. They are however, useful means of providing free water for, once the glucose is metabolised, they are largely distributed through total body water with very limited and transient effects on blood volume. They should therefore be useful in

correcting or preventing simple dehydration, and the administration of appropriate glucose saline with potassium solutions may provide a good means of meeting routine maintenance needs. However, the use of these fluids will increase risks of significant hyponatraemia, especially if too much fluid is given or the infusion is given too rapidly. Such risks are particularly high in children, the elderly, patients on diuretics and those with SIADH problems which are seen quite frequently in hospitalized patients. It is also important to appreciate that the calorie content of 5% glucose is very low and provides little contribution to the nutrition support which may be needed in some patients.

Synthetic Colloids

Synthetic colloids contain non-crystalline large molecules or ultramicroscopic particles dispersed through a fluid which is usually a crystalloid. The colloidal particles are large enough that they should be retained within the circulation and so exert an oncotic pressure across capillary membranes. In theory, colloids that are iso-oncotic with plasma should therefore expand blood volume by the volume infused but in practice, the volume expansion achieved is closer to 60-80%[7,62] and it may be much less in sicker patients with high transcapillary escape rates. The actual advantages of colloids over crystalloids when used for either intravascular volume expansion in patients requiring fluids for resuscitation or to help with the resolution of oedematous redistribution problems are therefore uncertain and with some preparations, there have been concerns that any potential advantages may be offset by problems including renal dysfunction or disturbed coagulation. It is important to note, that older preparations of hydroxyethyl starch are suspended in sodium chloride 0.9% while some newer preparations are suspended in balanced solutions which should make them more 'physiological'. Nevertheless, all currently available semi-synthetic colloids contain 140-154 mmol sodiumwhich could contribute to positive sodium balance in sicker patients in the same way as for sodium chloride 0.9%, although colloids do contain less chloride.

In the UK, synthetic colloids commonly used in admission and general ward areas include; hydroxyethyl starch, succinylated gelatin, urea-linked gelatin , whilst dextrans and high molecular weight penta- and hexa-starches are used seldom or not at all.

Albumin solutions

As with synthetic colloids, infusion of albumin solutions might theoretically grant potential benefits from better intravascular volume expansion although costs would be very high. Concentrated (20-25%) sodium poor albumin could also be valuable in fluid redistribution problems especially when oedema from total sodium and water overload is present in post- severe illness or injury patients who still have low plasma volumes.[3,4,54]Albumin is also used in some patients with hepatic failure and ascites although its use in this setting is beyond the scope of this guidance.

5.1.5 Recommendations based on fluid prescribing principles

Recommendations	**The assessment and management of patients' fluid and electrolyte needs is fundamental to good patient care.** **1. Assess and manage patients' fluid and electrolyte needs as part of every ward review. Provide intravenous (IV) fluid therapy only for patients whose needs cannot be met by oral or enteral routes, and stop as soon as possible.** **2. Skilled and competent healthcare professionals should prescribe and administer IV fluids, and assess and monitor patients receiving IV fluids (see recommendations 26-28).**

	3. When prescribing IV fluids, remember the 5 Rs: Resuscitation, Routine maintenance, Replacement, Redistribution and Reassessment. **4. Include the following information in IV fluid prescriptions:** • **The type of fluid to be administered.** • **The rate and volume of fluid to be administered.** **5. Patients should have an IV fluid management plan, which should include details of:** • **the fluid and electrolyte prescription over the next 24 hours** • **the assessment and monitoring plan.** **Initially, the IV fluid management plan should be reviewed by an expert daily. IV fluid management plans for patients on longer-term IV fluid therapy whose condition is stable may be reviewed less frequently.** **6. When prescribing IV fluids and electrolytes, take into account all other sources of fluid and electrolyte intake, including any oral or enteral intake, and intake from drugs, IV nutrition, blood and blood products.** **7. Patients have a valuable contribution to make to their fluid balance. If a patient needs IV fluids, explain the decision, and discuss the signs and symptoms they need to look out for if their fluid balance needs adjusting. If possible or when asked, provide written information (for example, NICE's Information for the public), and involve the patient's family members or carers (as appropriate).**
Relative values of different outcomes	Mortality and morbidity were identified as the most critical outcomes. The other outcome considered important for decision making was length of stay in hospital.
Trade-off between clinical benefits and harms	Given the morbidity associated with injudicious prescription of intravenous fluids, particularly the consequences of fluid overload (e.g. pulmonary oedema), the GDG agreed that emphasis should be placed on careful assessment and reassessment of the need for intravenous fluid therapy.
Economic considerations	There was no cost-effectiveness evidence. However, the principle of only using intravenous fluids when necessary and stopping them as early as possible is likely to be highly cost-effective, since it should both reduce the cost of administering unnecessary IV fluids and should reduce the cost of treating avoidable fluid overload as well as improving other clinical outcomes.
Quality of evidence	The GDG drafted these recommendations based on physiological, pathophysiological and clinical principles using consensus.
Other considerations	It was acknowledged that that it was not possible to undertake clinical evidence reviews for certain areas of the guideline and the principles of fluid prescribing was one such exception to the normal systematic review process. Here, the GDG took into consideration the principles of physiology and pathophysiology of intravenous fluids and other accepted standard clinical guidance and drafted recommendations based on expert consensus in a format intended to be useful to a clinician. The GDG discussed and agreed that as the recommendations were fundamental to fluid prescribing, the wording of the recommendations should reflect the strength of the recommendations.

	Clinical assessment and diagnosis of the volume status of the patient was judged to be key to prescribing safe, appropriate IV fluid therapy for a patient. The GDG discussed the four states where intravenous fluid was given, that is, (i) resuscitation, (ii) routine maintenance, iii) replacement of existing deficits or abnormal ongoing losses and iv) complex issues of redistribution. They agreed that clear identification of the reason for giving IV fluid therapy should always precede administration. Recommendations 3 and 5 were identified as key priorities for implementation by the GDG as they have a high impact on outcomes that are important to patients and have a high impact in reducing variation in care and outcomes.

5.2 Use of algorithms in IV fluid therapy

An approach to IV fluid prescribing based on physiological, pathophysiological and clinical principles can potentially be described in protocols and algorithms. Since it is well recognized that adoption of protocol- driven care has improved clinical standards in other areas, a review of the clinical and cost effectiveness of any published clinical algorithms or defined protocols for assessment, monitoring and/or management of IV fluid prescriptions was undertaken.

5.2.1 Review question

What is the clinical and cost effectiveness of clinical algorithms or defined protocols for the assessment, monitoring and/or management of intravenous fluid and electrolyte requirement in hospitalised adult patients?

The objective of this review was to compare outcomes in hospitalised patients who received IV fluid therapy as part of a protocol to those who received IV fluids without any protocol.

For the review protocol see C.1, Appendix C.

5.2.2 Clinical evidence

We searched for randomised controlled trials comparing the effectiveness of using algorithms or defined protocols compared to no protocols or usual care for the management of hospitalised adult patients on IV fluid therapy.

No Cochrane reviews relevant to the review question were identified.

Six randomised controlled studies were identified.[9,32,40,53,78,91] The studies included different populations and settings, for example; surgical patients, sepsis patients, burn patients and patients in intensive care units. Some of these studies did not meet the criteria set in the protocol for our target population, but in view of the paucity of directly relevant literature data, they were still extracted and extrapolated to our target groups, with the evidence downgraded for indirectness (see clinical evidence profile in Table 12).

All 6 studies compared protocol directed care with no protocol. The components of the protocols varied across the studies. Three studies focused on early goal directed therapy.[48,53,91] Table 11 details the summary characteristics of included studies.

Table 11: Summary of included studies - Protocol vs. no protocol

STUDY	POPULATION	INTERVENTION	COMPARISON	OUTCOMES
Benes et al. 2010[9]	High risk patients scheduled for major abdominal surgery	Protocol: Intraoperative; continuous monitoring of haemodynamic status using online analysis of arterial waveform. Perioperative: monitoring of stroke volume and cardiac index	No protocol: Anaesthesiologist free to give additional fluids (crystalloid or colloid) or use vasoactive substances to maintain blood pressure, diuresis and central venous pressure	Mortality, length of stay in hospital, morbidity and complications (sepsis, renal complications)
Gan et al. 2002[32]	Patients undergoing major elective surgery with an anticipated blood loss of >500mL	Protocol- Boluses of fluid guided by algorithm Doppler estimations of stroke volume.	No protocol: Standard care	Length of stay(hospitalisation), acute renal dysfunction, respiratory support for >24 hours, cardiovascular complications
Hopkins et al. 1983[40]	Hypotensive adults in surgical emergency department	Protocol for the first hour of resuscitation of emergency admissions	No protocol	All cause mortality, length of stay in hospital, resuscitation time, ICU days, complications related to shock and resuscitation
Lin et al. 2006[53]	Sepsis with organ failure, shock	Goal directed therapy: CVP of 8-12mmHg Mean arterial pressure ≥65mmHg	No protocol: Standard therapy adjusted by a physician	All cause mortality, total length of stay, length of ICU stay, duration of mechanical ventilation, sepsis associated renal failure
Noblett et al. 2006[78]	Elective colorectal resection Intra-operative and post-operative care	Additional fluids boluses given to maintain descending aortic corrected flow time > 0.35s stroke volume	Standard care Fluid administered by the anaesthetist based on intraoperative losses and standard haemodynamic parameters.	Mortality, total post-operative stay, post-operative complications requiring pharmacological management/ surgical/ endoscopic/ radiological intervention, life threatening complications requiring critical care
Rivers et al. 2001[91]	Patients with sepsis	Early goal directed therapy	No protocol: Standard therapy	All cause mortality, 28 day mortality, 60 day mortality, length of stay, quality of life, mean duration of mechanical ventilation.

Since the evidence came from different populations and settings, pooling of results across all studies was not considered to be appropriate. The evidence is therefore presented with respect to the different population sub-groups as identified in the review protocol.

See flow diagram for clinical article selection in J.1, Appendix J and economic article selection K.1, Appendix K, forest plots in G.1, Appendix G, clinical evidence tables in E.1, Appendix E, economic evidence tables in F.1, Appendix F and excluded studies list in H.1, Appendix, H.

Table 12: Clinical evidence profile: Protocol vs. No protocol

Quality assessment							No. of patients		Effect size			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Protocol	No protocol	Relative effect (95% CI)	Absolute effect	Quality	Importance
Mortality												
Sepsis patients[53,91]												
2	randomised trials	serious (a)	no serious inconsistency	serious indirectness(b)	no serious imprecision	none	94/238 (39.5%)	139/249 (55.8%)	RR 0.71 (0.59 to 0.86)	162 fewer per 1000 (from 78 fewer to 229 fewer)	LOW	CRITICAL
Intra-operative patients[9,78]												
2	randomised trials	serious (c)	no serious inconsistency	serious (b)	very serious (d)	none	1/114 (0.9%)	3/114 (2.6%)	RR 0.43 (0.06 to 2.85)	15 fewer per 1000 (from 25 fewer to 49 more)	VERY LOW	CRITICAL
Trauma/shock patients [40]												
1	randomised trials	serious (e)	no serious inconsistency	serious indirectness(b)	very serious (d)	none	39/212 (18.4%)	75/391 (19.2%)	RR 0.96 (0.68 to 1.36)	8 fewer per 1000 (from 61 fewer to 69 more)	VERY LOW	CRITICAL
Length of stay in hospital												
Sepsis patients[53,91]												
2	randomised trials	serious (a)	no serious inconsistency	serious indirectness(b)	very serious (d)	none	238	249	-	MD 2.09 lower (5.16 lower to 0.98 higher)	VERY LOW	IMPORTANT
Intra-operative patients[32]												
1	randomised trials	serious (f)	no serious inconsistency	serious indirectness(b)	no serious imprecision	none	50	50	-	MD 2 lower (3.18 to 0.82 lower)	LOW	IMPORTANT
Post-operative patients[48]												
1	randomised trials	very serious (g)	no serious inconsistency	serious indirectness(b)	no serious imprecision	none	15	15	-	MD 3 lower (4.22 to 1.78 lower)	VERY LOW	IMPORTANT
Trauma/Shock patients[40]												
1	randomised trials	serious (e)	no serious inconsistency	serious indirect	very serious (d)	none	173	316	-	MD 1 lower (4 lower to 2 higher)	VERY LOW	IMPORTANT

Quality assessment							No. of patients		Effect size			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Protocol	No protocol	Relative effect (95% CI)	Absolute effect	Quality	Importance
				ness(b)								
Length of stay in intensive care unit												
Trauma/Shock patients[40]												
1	randomised trials	serious (e)	no serious inconsistency	serious indirectness(b)	very serious (d)	none	173	316	-	MD 0 higher (1.81 lower to 1.81 higher)	VERY LOW	IMPORTANT
Post-operative patients[48]												
1	randomised trials	very serious (g)	no serious inconsistency	serious indirectness(b)	no serious imprecision	none	15	15	-	MD 2.3 lower (3.32 to 1.28 lower)	VERY LOW	IMPORTANT
Renal complications												
Sepsis patients[53]												
1	randomised trials	serious (a)	no serious inconsistency	serious indirectness(b)	serious (h)	none	42/108 (38.9%)	64/116(55.2 %)	RR 0.70 (0.53 to 0.94)	166 fewer per 1000 (from 33 fewer to 259 fewer)	VERY LOW	IMPORTANT
Intra-operative patients [9,32]												
2	randomised trials	serious (c, f)	no serious inconsistency	serious indirectness(b)	very serious (d)	none	5/110 (4.5%)	3/117 (2.7%)	RR 1.67 (0.41 to 6.75)	18 more per 1000 (from 16 fewer to 157 more)	VERY LOW	IMPORTANT
Post-operative patients[48]												
1	randomised trials	very serious (g)	no serious inconsistency	serious indirectness(b)	very serious (d)	none	1/15 (6.7%)	1/15 (6.7%)	RR 1 (0.07 to 14.55)	0 fewer per 1000 (from 62 fewer to 903 more)	VERY LOW	IMPORTANT

(a) One study was an open label study[53]and the follow up in the second study was unclear [91]; Also this study had >10% dropout rate.
(b) Studies were in indirect populations which may not be representative of all populations addressed in the guideline.
(c) One study was partially blinded and had >10% dropout rate [9] and in the second study, randomisation and allocation concealment were unclear(Noblett2006)
(d) Confidence interval crosses both MIDs
(e) The study participants did not adhere to the protocol at all times, ITT analysis not carried out, length of follow up not stated[40]
(f) Anaesthetist not blinded; Patients in protocol group received significantly more 6%HES than the standard care group; Different types of fluid administered in both groups[32]
(g) Small sample size, unblinded study, no ITT analysis[48]
(h) Confidence interval crosses one MID

.

5.2.3 Economic evidence

Three studies were included that made relevant comparisons. These are summarised in the economic evidence profile below (**Table 13** and **Table 14**)

See also the full study evidence table in F.1, Appendix F.

Table 13: Protocol vs No Protocol Economic Evidence

Study	Applicability	Limitations	Other comments
Jones [46]	Partially Applicable (a)	Potentially Serious Limitations (b)	Analysis conducted from a US perspective
Shorr[101]	Partially Applicable(a)	Potentially Serious Limitations(c)	Analysis conducted from a US perspective
Talmor [107]	Partially Applicable(a, d)	Potentially Serious Limitations(e)	Analysis conducted from a US perspective

(a) United States setting.
(b)Outcomes did not include all fluid related adverse events; Observational evidence which is subject to confounding; protocol did not exclusively manage IV fluid therapy; Long term costs not accounted for because patients were not followed beyond hospital discharge; uncertainty in components of non protocolised care which makes interpretation of results difficult.
(c)Observational evidence which is subject to confounding; Outcomes did not include all fluid related adverse event; Long term costs not accounted for due to lack of data ; protocol did not exclusively manage IV fluid therapy; uncertainty in components of non protocolised care which makes interpretation of results difficult.
(d)Protocol did not exclusively manage IV fluid therapy;
(e)Outcomes did not include all fluid related adverse events; management protocol not specific to intravenous fluid therapy; Long term costs not accounted for because patients were not followed beyond hospital discharge; Observational evidence which is subject to confounding; uncertainty in components of non protocolised care which makes interpretation of results difficult.

Table 14: Protocol vs. No Protocol -- Economic summary of findings

Study	Incremental cost	Incremental effects	ICER	Uncertainty
Jones [46]	£4,407[a]	1.3 QALYs gained	£3,384 per QALY gained	Results were not sensitive to utility of survivors or discount rate. Probability of cost-effectiveness was 97% at a threshold of £20,000 per QALY gained.
Shorr[101]	-£3,742[b]	-18% mortality	Protocol dominates (is less costly with lower mortality)	Not considered.
Talmor [107]	£5,568[c]	0.540 QALYs gained	£10,312 per QALY gained	If utility of survivors <0.4[d] then the ICER is >£20,000 and is not cost effective (base case=0.69)

a) converted to UK£from US$ using 2006 purchasing power parities (see Appendix F for full details)
b) converted to UK£from US$ using 2005 purchasing power parities (see Appendix F for full details)
c) converted to UK£ from US$ using 2004 purchasing power parities (see Appendix F for full details)

d) 0.4 is approximate since it was read off a graph (and then converted to UK£).

5.2.4 Evidence statements

Clinical evidence

Patients with sepsis

- Evidence from two studies in patients with sepsis suggested that patients receiving IV fluid therapy as part of a protocolised care package had less mortality, decreased length of hospital stay, and fewer renal complications compared to patients who received IV fluids not as part of any protocol. The quality of evidence was of low to very low quality.

Intra-operative patients

- Evidence from two studies in intra-operative patients suggested that patients receiving IV fluid therapy as part of a protocolised care package may have decreased mortality and decreased length of stay in hospital compared to patients who received IV fluids not as part of any protocol. The evidence was of very low quality.

Post-operative patients

- Evidence from one study in post-operative patients showed that patients receiving IV fluid therapy as part of a protocolised care package have decreased length of stay in hospital and intensive care unit compared to those receiving IV fluids not as part of any protocol. However, there was no difference with respect to number of renal complications between the two groups. The evidence was of very low quality.

Trauma/shock patients

- Evidence from one study in patients with trauma or shock suggested that there was no difference with respect to mortality, length of stay in hospital and length of stay in intensive care unit when comparing patients receiving IV fluid therapy as part of a protocolised care package with those who receive IV fluids not as part of any protocol. The evidence was of very low quality.

Economic evidence

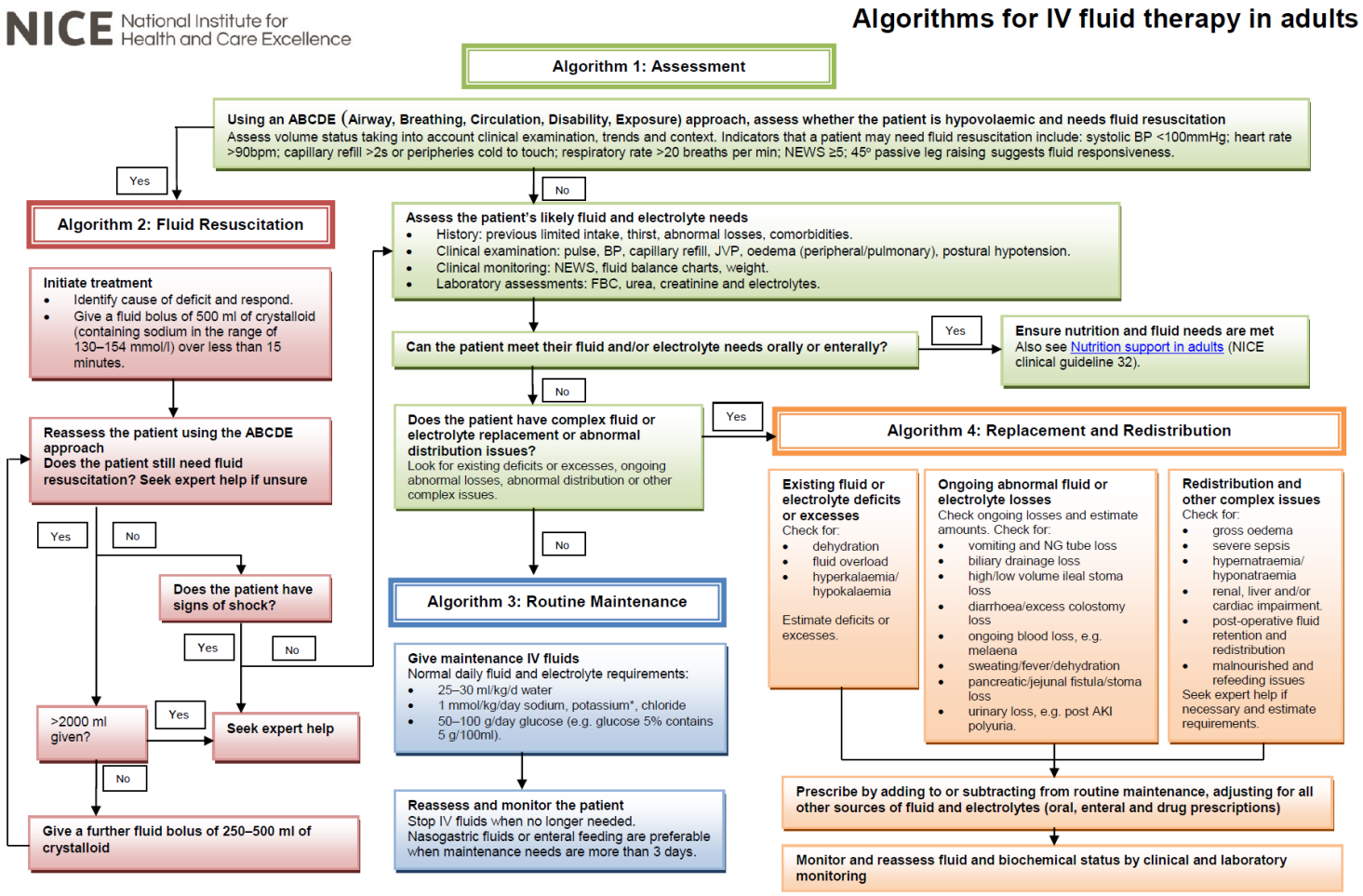
- Three studies found that compared to conventional, non- protocolised care, IV fluid therapy as part of a protocolised care package for patients presenting with sepsis and septic shock was cost effective (from cost saving up to £10,312 per QALY gained). This analysis was assessed as partially applicable with potentially serious limitations.

5.2.5 Recommendations and link to evidence

Recommendations	**8. Offer IV fluid therapy as part of a protocol (see Algorithms for IV fluid therapy):** • **Assess patients' fluid and electrolyte needs following Algorithm 1: Assessment.** • **If patients need IV fluids for fluid resuscitation, follow Algorithm 2: Fluid Resuscitation.** • **If patients need IV fluids for routine maintenance, follow Algorithm 3: Routine maintenance.** • **If patients need IV fluids to address existing deficits or excesses, ongoing abnormal losses or abnormal fluid distribution, follow Algorithm 4: Replacement and redistribution.**

Relative values of different outcomes	Mortality and morbidity were identified as the most critical outcomes. Length of stay in hospital was also considered important for decision making was.
Trade-off between clinical benefits and harms	The clinical evidence review found that on the whole, outcomes, including survival were more favourable in patients receiving IV fluids as part of a protocol-based care package, irrespective of different patient population groups, that is, patients with sepsis or intra/post-operative patients. It was recognised that components of individual protocols influence outcomes differently in different populations and this should be kept in mind when following any particular protocol. The GDG agreed that emphasis should be placed on accurate assessment and reassessment of volume and electrolyte status when administering IV fluid therapy to any patient.
Economic considerations	In patients with sepsis, IV fluid therapy as part of a protocolised care package was found to be cost-effective for sepsis patients in two studies and cost saving in a third study. There was no cost-effectiveness evidence for patients without sepsis. However, given that the health improvements observed in the review of clinical effectiveness evidence were just as pronounced for intra-operative care the GDG felt that the economic benefits of protocols are very likely to be achievable across all settings. However, there were issues of applicability and quality – see below.
Quality of evidence	The quality of the clinical evidence varied from low to very low. The studies included in the clinical evidence review have several limitations and are at risk of bias. Since our target population is all hospitalised patients, the clinical evidence available from the studies found for specific population groups has limited applicability and the evidence has been downgraded for indirectness. The three cost-effectiveness evidence studies were all in a US setting and therefore may not be transferable to a UK NHS setting since clinical practice resource use and unit costs are all likely to be different. In addition there were some potentially serious limitations. For example, not all health and cost outcomes of interest were included and unlike the clinical evidence reviewed above all three were based on observational evidence.
Other considerations	The GDG discussed that evidence was only available for specific population groups which may not applicable to all hospitalised patients, particularly older patients with multiple co-morbid chronic diseases. The GDG also discussed the extreme heterogeneous nature of the target population and agreed that it would not be meaningful to pool the evidence across different population groups. Results are therefore presented separately. Nevertheless, the evidence favoured the use of protocolised care when giving IV fluids, irrespective of the population group, and the GDG were not only aware that following of protocols has been shown to be of value in several other areas of complex decision making in healthcare, but felt that algorithms were the best way for the guidance to be implemented across hospital settings. The GDG therefore made a consensus decision to advocate the use of algorithms for IV fluid therapy. In view of the above, the GDG drafted four algorithms to be used for management of IV fluid therapy in hospitalised patients covering: assessment (algorithm 1); fluid resuscitation (algorithm 2); routine maintenance (algorithm 3); and replacement and redistribution (algorithm 4). Available evidence and discussion underpinning steps in each of the individual algorithm is presented in the relevant sections. This recommendation was identified as a key priority for implementation by the GDG.

5.2.6 Algorithms for IV fluid therapy


NICE National Institute for Health and Care Excellence
Algorithms for IV fluid therapy in adults
Algorithm 1: Assessment
Using an ABCDE (Airway, Breathing, Circulation, Disability, Exposure) approach, assess whether the patient is hypovolaemic and needs fluid resuscitation
Assess volume status taking into account clinical examination, trends and context. Indicators that a patient may need fluid resuscitation include: systolic BP <100mmHg; heart rate >90bpm; capillary refill >2s or peripheries cold to touch; respiratory rate >20 breaths per min; NEWS ≥5; 45° passive leg raising suggests fluid responsiveness.
Yes
No
Algorithm 2: Fluid Resuscitation
Initiate treatment
Identify cause of deficit and respond.
Give a fluid bolus of 500 ml of crystalloid (containing sodium in the range of 130–154 mmol/l) over less than 15 minutes.
Reassess the patient using the ABCDE approach
Does the patient still need fluid resuscitation? Seek expert help if unsure
Yes
No
Does the patient have signs of shock?
Yes
No
>2000 ml given?
Yes
Seek expert help
No
Give a further fluid bolus of 250–500 ml of crystalloid
Assess the patient's likely fluid and electrolyte needs
History: previous limited intake, thirst, abnormal losses, comorbidities.
Clinical examination: pulse, BP, capillary refill, JVP, oedema (peripheral/pulmonary), postural hypotension.
Clinical monitoring: NEWS, fluid balance charts, weight.
Laboratory assessments: FBC, urea, creatinine and electrolytes.
Can the patient meet their fluid and/or electrolyte needs orally or enterally?
Yes
Ensure nutrition and fluid needs are met
Also see Nutrition support in adults (NICE clinical guideline 32).
No
Does the patient have complex fluid or electrolyte replacement or abnormal distribution issues?
Look for existing deficits or excesses, ongoing abnormal losses, abnormal distribution or other complex issues.
Yes
Algorithm 4: Replacement and Redistribution
No
Algorithm 3: Routine Maintenance
Give maintenance IV fluids
Normal daily fluid and electrolyte requirements:
25–30 ml/kg/d water
1 mmol/kg/day sodium, potassium*, chloride
50–100 g/day glucose (e.g. glucose 5% contains 5 g/100ml).
Reassess and monitor the patient
Stop IV fluids when no longer needed.
Nasogastric fluids or enteral feeding are preferable when maintenance needs are more than 3 days.
Existing fluid or electrolyte deficits or excesses
Check for:
dehydration
fluid overload
hyperkalaemia/ hypokalaemia
Estimate deficits or excesses.
Ongoing abnormal fluid or electrolyte losses
Check ongoing losses and estimate amounts. Check for:
vomiting and NG tube loss
biliary drainage loss
high/low volume ileal stoma loss
diarrhoea/excess colostomy loss
ongoing blood loss, e.g. melaena
sweating/fever/dehydration
pancreatic/jejunal fistula/stoma loss
urinary loss, e.g. post AKI polyuria.
Redistribution and other complex issues
Check for:
gross oedema
severe sepsis
hypernatraemia/ hyponatraemia
renal, liver and/or cardiac impairment.
post-operative fluid retention and redistribution
malnourished and refeeding issues
Seek expert help if necessary and estimate requirements.
Prescribe by adding to or subtracting from routine maintenance, adjusting for all other sources of fluid and electrolytes (oral, enteral and drug prescriptions)
Monitor and reassess fluid and biochemical status by clinical and laboratory monitoring

*Weight-based potassium prescriptions should be rounded to the nearest common fluids available (for example, a 67 kg person should have fluids containing 20 mmol and 40 mmol of potassium in a 24-hour period). Potassium should not be added to intravenous fluid bags as this is dangerous.

'Intravenous fluid therapy in adults in hospital', NICE clinical guideline 174 (December 2013. Last update December 2016)

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6 Assessment and monitoring of patients receiving intravenous fluid therapy

6.1 Introduction

Hospital patients needing IV fluids are very variable in terms of their current fluid and electrolyte status and their likely physiological responses to IV fluid therapy. They therefore need a full assessment by a competent clinician of the best content, volume and rate of IV fluids to be given in order to minimize risks of:

- Under- or over-provision of fluid and
- Electrolyte abnormalities such as hypo- or hyper-natraemia, hypo- or hyper-kalaemia and hyper-chloraemic acidosis.

Since these types of complications often lead to increased morbidity and mortality (e.g. pulmonary oedema increases risks of subsequent pneumonia whilst peripheral oedema increases risks of debilitating ulceration), careful assessments should also reduce length of stay and discomfort to patients.

Assessments should be based on the principles outlined in 5.1.2.3. The clinical approach to assessing IV fluid needs. These include a focussed history, clinical examination, inspection of monitoring charts and consideration of laboratory indices in terms of both current values and previous trends. Since it is not possible fully to predict how each patient will handle IV fluids when initiating therapy, the same elements need reassessment on a regular basis so that the IV fluid prescription can be altered as appropriate and stopped as soon as possible. The importance of this reassessment is highlighted in the recommendations as the 5th R in the 5R principle of IV fluid prescribing.

Undertaking assessments of IV fluid and electrolyte needs is not always straightforward and standards of practice are very variable in hospital admission and general ward areas. Even senior clinicians sometimes need guidance in the assessment of more complex patients e.g. those with significant oedema or abnormal gastrointestinal losses, yet despite the complexity of the process, it is often delegated to the most junior medical staff with no established process for senior review. Many of those juniors have also received little training in assessment of IV fluid needs and misinterpretation of indices which inform IV fluid prescription is common. For example, low serum sodium may lead an inexperienced doctor to prescribe a higher sodium containing fluid, even in the presence of volume overload when whole body sodium content is likely to be high. Indeed, the need for continuing IV fluids is not always questioned with some juniors inclined simply to repeat the previous day's IV fluid prescription rather than properly reassess the patient or seek advice from a senior colleague. Furthermore, the data that clinicians rely on to aid prescribing decisions, such as measures of urine output, other losses, oral input, fluids administered (including those with IV drugs), body weight and laboratory results, are often incomplete.

This chapter examines the different components of clinical and laboratory assessment to try to determine which are the most important to ensure safe and effective IV fluid therapy. An algorithm to support decision-making is also suggested.

6.2 Assessment

6.2.1 Review question: What aspects of clinical assessment are required to assess, monitor and re-evaluate fluid and electrolyte status?

The GDG agreed that a formal clinical evidence approach to this question was not appropriate as the rationale and justification for each aspect of clinical assessment was embedded in the principles and protocols for intravenous fluid therapy and could not be answered by a specific review question. Furthermore, there is evidence based guidance from NICE on the different aspects to be considered when assessing and monitoring patients (NICE guideline on 'Acutely ill patients in hospital' and the GDG.[16]The GDG drew upon this guidance when drafting the recommendations for this section.The GDG agreed that no literature search would be undertaken and the guidance would be based on consensus using the expert opinion of GDG members and the principles of fluid prescribing as described in the section on Principles and protocols for intravenous fluid therapy, along with reference to NICE guideline on 'Acutely ill patients in hospital' [16] which identifies the main areas of clinical assessment and physical examination that are important to IV fluid management.

The guidance would also take into account the National Early Warning Score (NEWS).[95]The National Early Warning Score (NEWS) is a Department of Health initiative which was accepted by the GDG as a reliable and informative scoring system for assessment. NEWS has been demonstrated to be as good as the best of other early warning scores in discriminating risk of acute mortality and is likely to be more sensitive than most currently used systems at prompting an alert and clinical response to acute illness deterioration.[95]

However, the GDG did identify a number of review questions on specific issues of laboratory or ward-based assessments, pertinent to assessment and monitoring and three of these were felt to be in areas where there was high variation in practice and a lack of clear guidance. These were therefore prioritised by the GDG for formal clinical evidence reviews to inform decision-making. The three areas were:

- Serial measurement of body weight
- Measurement of urinary output and recording fluid balance
- Measurement of serum chloride levels

A review conducted earlier in the guideline which evaluated the clinical and cost effectiveness of using an algorithm to guide care, found evidence to support the use of algorithms and the GDG have therefore suggested an algorithmic approach to the assessment and monitoring of patients receiving IV fluids (see section 5.2)

Recommendations	**9. Assess whether the patient is hypovolaemic. Indicators that a patient may need urgent fluid resuscitation include:** • **systolic blood pressure is less than 100 mmHg** • **heart rate is more than 90 beats per minute** • **capillary refill time is more than 2 seconds or peripheries are cold to touch** • **respiratory rate is more than 20 breaths per minute**

	• **National Early Warning Score (NEWS) is 5 or more** • **passive leg raising suggests fluid responsiveness[f].** **10. Assess the patient's likely fluid and electrolyte needs from their history, clinical examination, current medications, clinical monitoring and laboratory investigations:** • **History should include any previous limited intake, thirst, the quantity and composition of abnormal losses (see Diagram of ongoing losses), and any comorbidities, including patients who are malnourished and at risk of refeeding syndrome (see Nutrition support in adults [NICE clinical guideline 32]).** • **Clinical examination should include an assessment of the patient's fluid status, including:** – pulse, blood pressure, capillary refill and jugular venous pressure – presence of pulmonary or peripheral oedema – presence of postural hypotension. • **Clinical monitoring should include current status and trends in:** – NEWS – fluid balance charts – weight. • **Laboratory investigations should include current status and trends in:** – full blood count – urea, creatinine and electrolytes.
Relative value of different outcomes	Six physiological parameters are routinely monitored in hospital (i) respiratory rate, (ii) oxygen saturations, (iii) temperature, (iv) systolic blood pressure, (v) pulse rate and (vi) level of consciousness. These form the basis of the National Early Warning Score (NEWS) upon which the GDG has based its recommendations.[95] Assessment of volume status also requires additional assessments or measurements of body weight, fluid balance, jugular venous pressure and the presence or absence of fluid-related complications, as well as laboratory measures of FBC, urea, creatinine and electrolytes. The GDG agreed that serial, accurate assessment or measurement of all these additional parameters provides important information for assessing volume status and estimating the need for fluid and electrolytes.
Trade-off between benefits and harms	Routine laboratory assessment of patients on intravenous therapy may require additional blood tests to be taken from the patient. However, the GDG agreed that serial measurement of biochemical markers can provide important additional information on renal function and potential complications of fluid therapy (e.g. chloride load).
Economic evidence	Time and resources spent on monitoring fluid status are crucial to good patient care and are likely to be more than offset by health gains and potential cost

f Passive leg raising is a bedside method to assess fluid responsiveness in a patient. It is best undertaken with the patient initially semi-recumbent and then tilting the entire bed through 45°. Alternatively it can be done by lying the patient flat and passively raising their legs to greater than 45°. If, at 30–90 seconds, the patient shows signs of haemodynamic improvement, it indicates that volume replacement may be required. If the condition of the patient deteriorates, in particular breathlessness, it indicates that the patient may be fluid overloaded.

	savings from complications averted. The monitoring strategies recommended here are commonly practiced in the NHS.
Quality of evidence	Recommendations were drafted based on principles of fluid prescribing, NICE guidance CG50 'Acutely ill patients in hospital' [16], the NEW score [95] and consensus expert opinion of the GDG members. NEWS has been demonstrated to be as good as the best of other early warning scores in discriminating risk of acute mortality and is likely to be more sensitive than most currently used systems at prompting an alert and clinical response to acute illness deterioration. [95]. The recommendations in the NICE guideline on acutely ill patients in hospital were based on systematic literature reviews of the evidence and consensus opinion of the GDG members of that guideline, if no evidence was identified.[16]
Other considerations	In considering the question of optimal assessment and reassessment the GDG aimed for recommendations that ensure IV fluid therapy delivers its therapeutic purpose whilst complications are prevented or identified as soon as possible. The GDG discussed the fact that interpretation of commonly used assessment tools (e.g serum sodium and potassium levels) is poor amongst junior medical staff and can lead to poor IV fluid prescribing. They therefore concluded that assessment issues must also be included in the training and education arm of this guidance (see section on Training and education of health care professionals for management of intravenous fluid therapy) The GDG acknowledged that there are significant practical challenges in measuring certain clinical parameters. For example, serial assessment of body weight in obese or bedbound patients requires additional resources of time and staff. Similarly, the GDG agreed that recording of fluid intake and output is often incomplete or inaccurate on fluid balance charts. Despite these challenges, the GDG felt it important to emphasise the value of serial body weights and accurate fluid balance records in monitoring response to intravenous fluid therapy and identification of potential harm, specifically fluid overload. The GDG agreed that recommendation 9 was a key priority for implementation.

6.3 Reassessment and monitoring

Evidence reviews were undertaken in the three areas prioritised by the GDG:

- Serial measurement of body weight
- Measurement of urinary output and recording fluid balance
- Measurement of serum chloride levels

6.3.1 Serial measurement of body weight

Regular, accurate measurement of the patient's weight can be a useful indicator of inadequate or excessive volume replacement. However, even with modern equipment, documenting accurate weight changes can be difficult. There are particular difficulties with non-ambulant and obese patients and post-operative patients with pain control issues and numerous lines and drains. Baseline weights are rarely accurate and the measurements are subject to numerous confounders, such as the external losses into drains and dressings, and potentially huge volumes of fluid can be redistributed in oedema or sequestered within a non-functioning gut or the natural body cavities. The GDG examined the published literature to determine whether there was any evidence to support the need for repeated body weight measurements in patients in general, as well as in specific high risk groups such as those with chronic kidney disease or heart failure.

6.3.1.1 Review question

In hospitalised patients receiving IV fluids, what is the clinical and cost effectiveness of measuring and recording serial body weight?

We searched for systematic reviews, randomised controlled trials and cohort studies comparing the effectiveness of the clinical and cost effectiveness for measuring and recording serial weights compared to any one or more of the following:

- Usual care (i.e. where there is no specific protocol to measure and record weight)
- fluid balance chart
- weight measurement plus fluid balance chart
- clinical assessment.

The GDG had identified patients with chronic renal impairment or congestive heart failure as specific subgroups who would benefit more from weighing due to pathophysiological changes in their fluid handling.

For more details see review protocol in C.2.1, Appendix C.

6.3.1.2 Clinical evidence

No studies were found on the use of serial weight measurement to inform the clinical monitoring of IV fluid administration in hospitalised patients.

For details on excluded studies, see section H.2, Appendix H.

6.3.1.3 Economic evidence

No published studies of cost-effectiveness were found. The GDG considered monitoring to be a high priority for de novo economic modelling. However, the clinical review did not find evidence of clinical effectiveness, so a simple cost analysis was conducted with a threshold sensitivity analysis around the number of complications averted, see Appendix L. We considered different strategies that were differentiated by the frequency of weighing patients and the presence or absence of fluid chart use.

It was assumed that weighing would be predominantly done by health care assistants whereas fluid balance would predominantly be done by nurses. The cost of weighing a patient was estimated to be £11 each time (ranging from £2 for a mobile patient to £25 for a completely immobile patient) and the cost of routinely completing a fluid balance chart was estimated to cost £20 per patient per 24hr day (34 minutes per patient).

The cost of a major fluid-related complication (see 4.2.3) was estimated using NHS reference costs to be £1868 (or £3,000 including a critical care episode).

The cost of each monitoring strategy is shown in Table 15 along with the number of complications that would need to be averted to make each strategy cost neutral.

This analysis can be considered as partially applicable (since NHS unit costs were used but QALYs were not estimated) but it has potentially serious limitations since the resource use was based on expert opinion. Furthermore, conclusions about cost-effectiveness or cost neutrality are not possible without evidence of the number of complications averted due to monitoring.

Table 15: The cost of monitoring

Strategy		Total costs for each monitoring strategy per week (£)	Number of extra major complications that would have to be avoided per 1000 patients (g) to make strategy cost neutral compared to no monitoring (including cost of critical care)
Weight	**Fluid Balance Chart**		
none	no fluid chart	£0	---
twice a week	no fluid chart	£16	8 (5)
daily	no fluid chart	£55	30 (18)
none	fluid chart	£102	54 (34)
twice a day	no fluid chart	£111	59 (37)
twice a week	fluid chart	£118	63 (39)
daily	fluid chart	£157	84 (52)
twice a day	fluid chart	£213	114 (71)

(a) Patients hospitalised for five days

6.3.1.4 Evidence statements

Clinical

No studies were found comparing the clinical and cost effectiveness of measuring and recording serial bodyweights compared to usual care, including no protocol to measure and record weight, fluid balance chart, weight measurement plus fluid balance chart or clinical assessment to inform the clinical monitoring of IV fluid administration in hospitalised patients.

Economic

An original comparative cost analysis showed that, if a strategy of weighing patients twice a week prevents 5-8 major complications per 1000 patients, then it would be cost neutral compared with no monitoring. This analysis was assessed as partially applicable with potentially serious limitations.

The same original comparative cost analysis showed that, if a strategy of weighing patients daily prevents 18-30 major complications per 1000 patients, then it would be cost neutral compared with no monitoring. This analysis was assessed as partially applicable with potentially serious limitations.

6.3.1.5 Recommendations and link to evidence

The assessment and monitoring of body weight is closely interlinked to the measurement of urinary output (as recorded by maintaining fluid balance charts). Therefore, reviews on both of these topics have been considered together and recommendations on both these aspects are combined, and presented at the end of the review on measurement of urinary output (see section 6.3.2.5)

6.3.2 Measurement of urinary output and recording of fluid balance

Regular, accurate monitoring of urine output is considered a standard of care for all patients receiving intravenous volume replacement although it is not one of the parameters measured as part of the NEWS scoring system.[82] As with the assessment of body weight (see above), variation in urine output requires interpretation within the clinical context; oliguria may not indicate hypovolaemia while polyuria may be seen regardless of the state of the intravascular space. [32,50,68,71,78,103,112,115]The GDG examined the evidence for regular measurement of urine output, in addition to the standard parameters of the NEWS scoring system, and its influence on outcome measures.[95]

6.3.2.1 Review question

In hospitalised patients receiving intravenous fluids, what is the clinical and cost effectiveness of measuring and recording urine output in addition to recording standard parameters stated in NEWS to determine the need for intravenous fluid administration?

We searched for systematic reviews, randomised controlled trials and cohort studies comparing the clinical and cost effectiveness of measuring and recording urine output in addition to recording standard parameters stated in NEWS to determine the need for IV fluid administration.

The GDG identified that achieving stable fluid balance may be more challenging in certain groups of patients namely individuals with chronic renal impairment and those at risk of acute kidney injury; those with congestive cardiac failure; older people and peri-operative patients. These were therefore identified as specific subgroups in whom additional benefit may be derived from having their urine output measured.

For more details see review protocol in section C.2.2 in Appendix C.

6.3.2.2 Clinical evidence

No studies were found on use of urinary output to inform the clinical need for IV fluid administration in hospitalised patients.

For details on clinical article selection and excluded studies, see section J.2 (Appendix J) and section H.2 (Appendix H) respectively.

6.3.2.3 Economic evidence

No published economic evidence was found on this question. A de novo comparative costing analysis was conducted comparing different monitoring strategies (see section 6.3.1.3).

6.3.2.4 Evidence statements

Clinical

No studies were found comparing the clinical and cost effectiveness of measuring and recording urinary output in addition to recording standard parameters stated in NEWS to inform the clinical need for IV fluid administration in hospitalised patients.

Economic

An original comparative cost analysis showed that, if systematically completing a fluid balance chart prevents 34-54 major complications per 1000 patients, then it would be cost neutral compared with no monitoring. This analysis was assessed as partially applicable with potentially serious limitations.

6.3.2.5 Recommendations and link to evidence

Recommendations	**11. If patients are receiving IV fluids for resuscitation, reassess the patient using the ABCDE approach (Airway, Breathing, Circulation, Disability, Exposure), monitor their respiratory rate, pulse, blood pressure and perfusion continuously, and measure their venous lactate levels and/or arterial pH and base excess according to guidance on advanced life support (Resuscitation Council [UK], 2011)[90].**
Relative value of different outcomes	The GDG agreed that all-cause mortality was the most critical outcome. Other outcomes such as morbidity (as measured by SOFA scores and MOD scores) were also important to decision making.
Trade-off between benefits and harms	The GDG considered that there were only benefits to monitoring and that this is part of standard care.
Economic considerations	Since patients requiring resuscitation are seriously ill, time spent carefully monitoring is likely to be offset considerably by health gains and potential cost savings from complications being averted.
Quality of evidence	Recommendations were drafted based on the NEW score, NICE guidance on management of critically ill patients in hospital and consensus expert opinion of the GDG members.[16,95]
Other considerations	The assessment of patients receiving IV fluid for resuscitation was considered separately as it was agreed by the GDG this is a short-term assessment protocol with a high degree of urgency required. The ABCDE approach to resuscitation is based on standard principles of resuscitation. Measurement of venous and/or arterial lactate was discussed by the GDG and it was agreed that this is now widely available in acute settings and part of Advanced Life Support and Advanced Trauma Life Support protocols and can guide IV fluid therapy decisions.[5]

Recommendations	**12. All patients continuing to receive IV fluids need regular monitoring. This should initially include at least daily reassessments of clinical fluid status, laboratory values (urea, creatinine and electrolytes) and fluid balance charts, along with weight measurement twice weekly. Be aware that:** • **Patients receiving IV fluid therapy to address replacement or redistribution problems may need more frequent monitoring.** • **Additional monitoring of urinary sodium may be helpful in patients with high-volume gastrointestinal losses. (Reduced urinary sodium excretion [less than 30 mmol/l] may indicate total body sodium depletion even if plasma sodium levels are normal. Urinary sodium may also indicate the cause of hyponatraemia, and guide the achievement of a negative sodium balance in patients with oedema. However, urinary sodium values may be misleading in the presence of renal impairment or diuretic therapy.)** • **Patients on longer-term IV fluid therapy whose condition is**

	stable may be monitored less frequently, although decisions to reduce monitoring frequency should be detailed in their IV fluid management plan. **13. Clear incidents of fluid mismanagement (for example, unnecessarily prolonged dehydration or inadvertent fluid overload due to IV fluid therapy) should be reported through standard critical incident reporting to encourage improved training and practice (see Consequences of fluid mismanagement to be reported as critical incidents).** **14. If patients are transferred to a different location, reassess their fluid status and IV fluid management plan on arrival in the new setting.**
Relative values of different outcomes	The GDG agreed that the most important outcomes are reduction of mortality and morbidity from fluid overload or dehydration from receiving insufficient fluid. Other important outcomes included reductions in respiratory or renal complications, length of hospitalisation and quality of life for the patient. These outcomes can be affected by the patient's fluid balance and serial weight changes are an indicator of this. Urinary output is an important element in the assessment of fluid balance and the adequacy of fluid provision. However, no evidence was found reporting these outcomes.
Trade-off between clinical benefits and harms	No studies were identified that investigated the additional benefit of measuring daily weight. Daily weight is an indicator of fluid accumulation or depletion and provides an indicator of whether a person is dehydrated or has received excessive fluids (overload); both of these states are associated with increased morbidity. Measuring daily weight improves the quality of patient care and potentially reduces morbidity and mortality in patients requiring IV fluids. No studies were identified that investigated the additional benefit of measuring urinary output. Urinary output is a key component of fluid balance in a person and provides an indicator of whether a person is dehydrated or has received too much fluid (overload); both of these states are associated with morbidity and mortality. Measurement of urinary output improves the quality of patient care and potentially reduces morbidity and mortality in patients requiring IV fluids. Measurement of spot urinary sodium can be useful in determining whether patients with potentially high sodium losses e.g. those with excessive upper GI losses from vomiting or high output stomas, may have whole body sodium depletion. When it will usually be very low (<30 mmol/L) whilst plasma sodium levels may be maintained. Results however, can be misleading in the presence of significant renal impairment. Urinary sodium measurements, combined with measures of urinary volume and estimates of the sodium content of all other abnormal losses, can also be of value in assessing net sodium balance in oedematous patients when achievement of net negative balance is often the aim. The GDG discussed that there may be difficulties in weighing patients who are immobile and the risks associated with this.
Economic considerations	There was no existing economic evidence and it was inappropriate to model given the lack of evidence of clinical effectiveness. Both serial weight measurement and completion of fluid balance charts add to the workload for nursing staff and healthcare assistants. An original cost threshold analysis indicated that, to be cost neutral, twice weekly weighing would only need to prevent 5-8 major complications per 1000

	patients, which seemed plausible to the GDG. Daily weights would need to prevent 18-30 major complications per 1000 patients, this seemed less likely to the GDG, especially in the context of systematic completion of fluid balance charts. Twice weekly weighing is believed to be common practice in the NHS and is used to assess nutritional status as well as fluid status. More frequent weighing could not be justified. Based on their collective experience, the GDG considered it very likely that systematic completion of fluid balance charts is cost-effective. For example they can be used to identify renal impairment as well as calculate fluid balance. They noted that the cost of monitoring patients receiving IV fluids seemed small relative to the cost of an inpatient stay, as a whole. Overall these recommendations reflect current practice. There was no evidence for increasing the intensity of monitoring but nor was there evidence to reduce intensity.
Quality of evidence	Serial weight: No studies were found which were relevant to this review protocol. The recommendations were based on the consensus opinion of the GDG members. Urinary output: No RCT or cohort studies investigating the clinical benefit of measuring urinary output among patients on IV fluid was found. The recommendations were based on the consensus opinion of the GDG members
Other considerations	Serial weights and measurement of urine output: The clinical review did not find any studies which directly met the criteria pre-specified in the review protocol. However, during the course of the review, several papers were highlighted which the GDG felt were particularly useful to aid them in developing recommendations based on consensus. Some of these studies were included for the reviews on fluid type or volume and timing.. The GDG noted the following findings from these studies: One study which recorded cumulative intake and output among patients found that these correlated with daily weights. However, fluid balance data were less reliable and accurate than daily weight. The study recommended using daily weight for all patients who did not have acute kidney injury.[123] Cumulative weight change also correlated with cumulative fluid balance in another study [94] and a similar trend was noticed for both fluid balance and weight change for patient undergoing cardiac surgery.[28] Weight gains were larger and of similar magnitude of the extra volumes of fluid given to the "liberal" arm in a study comparing "restricted" versus "liberal" fluid for perioperative colon resection patients.[55] One study evaluated the feasibility of use of beds with built in electronic weighing scales in the ICU and correlated the fluid balance estimated by this method with fluid balance estimated by regular charting of fluid input and output.[97]As with other studies, this study reported weak correlation between both these measurements and found that changes in body weight and fluid balance had wide limits of agreement. The study concluded that even with modern technology- based weighing beds and trained staff, obtaining reliable weights in ICU patients is difficult. One study which looked at accuracy of documentation of NEWS criteria prior to emergency admissions to intensive care unit found urinary output was the second worst documented criterion – only documented in 42% of patients.[47] The GDG also discussed the practicality and feasibility of weight measurements in hospitals and their optimal frequency, with specific discussion in relation to the difficulty in measuring weights in specific population groups such as obese patients and patients who were bed-bound. Despite the lack of RCT evidence and the considerable practical difficulties the GDG felt that the recommendation of twice weekly weight measurement and daily fluid balance

	charts for patients receiving IV fluids should be part of assessment and reassessment to aid decision making when prescribing IV fluids and to bring patients at risk of complications of IV fluid therapy to the attention of the clinical staff as early as possible. It is expected that weight measurements will be undertaken by scales that have been subjected to calibration protocols and are standardised across the hospital. The GDG agreed that recommendations 12 and 13 were key priorities for implementation. The GDG also discussed that the recommended frequency of 'at least daily' reassessment of clinical fluid status, laboratory values (urea, creatinine and electrolytes) and fluid balance charts was the minimal basic standard to be expected in monitoring of patients. This does not replace clinical judgement and decision making where this frequency may be increased depending on the clinical condition of the patient. The GDG discussed the current lack of emphasis on reporting of adverse outcomes occurring as a result of mismanagement of IV fluid therapy. It was believed that part of the reason for this was the fact that the complications have not been directly attributed to mismanagement of IV fluid therapy and there is a lack of understanding on how to how to diagnose these in the context of IV fluid management. The GDG recommended that complications occurring as a result of mismanagement should be reported as critical incidents. It was agreed that this recommendation would be supported by providing a framework on how to diagnose these complications in the context of IV fluid management and the GDG drafted a table through consensus detailing these to support the recommendation (see Consequences of fluid mismanagement to be reported as critical incidents).Due to the paucity of evidence in relation to reporting of complications related to intravenous fluid therapy, the GDG also prioritised a research recommendation in this topic area (see section 6.4)

6.3.3 Measurement of serum chloride

Hyperchloraemia is a recognised consequence of the intravenous fluid therapy and there is some evidence in the literature suggesting that it may be associated with higher levels of mortality and morbidity due to development of hyperchloraemic acidosis or reduced renal perfusion and glomerular filtration rates. Administration of intravenous fluids with concentrations of chloride higher than normal plasma levels will clearly predispose individuals to hyperchloraemia whilst, conversely, inadequate intravenous provision of chloride in patients with high GI losses may be associated with the development of hypochloraemia and hypochloraemic alkalosis. The measurement of plasma chloride concentration underlies the diagnosis of either hyperchloraemia or hypochloraemia but there are wide variations in practice as to whether this test is undertaken.

6.3.3.1 Review question

In hospitalised patients receiving intravenous fluids, what is the incidence and clinical significance of hyperchloraemia and hypochloraemia?

The evidence review aimed to evaluate the incidence of hyperchloraemia, hyperchloraemic acidosis and hypochloraemia in people receiving intravenous fluid therapy and the clinical significance of these problems, particularly their association with mortality and morbidity. The focus of the review was to address outcomes related to patient safety and the consequences of mismanagement of intravenous fluid therapy rather than on core clinical effectiveness outcomes.

The measurement of serum chloride is the gold standard in diagnosis of any abnormality in serum chloride level, but it was important to ascertain the clinical context in which this measurement is essential in addition to measurement of other biochemical parameters in patients receiving intravenous fluid therapy. It was recognised that all the relevant evidence in this topic area would not lend itself to most types of review protocol, for example, a diagnostic review, an intervention review or a prognostic review.

A two part approach was undertaken to address the objectives of this review and include allavailable relevant literature.

- The first section evaluated the incidence of hyperchloraemia or hyperchloraemic acidosis in patients receiving fluids containing different concentrations of chloride. Randomised controlled trials were identified to be the most appropriate type of study design for this review. However, it was recognised that the evidence from RCTs will mainly be for short term outcomes. Therefore, evidence from cohort studies and case control studies was reviewed for this section only if long term outcomes were not presented in RCTs and the observational studies reported these outcomes. A summary of the studies presented in this section is presented in Table 16
- The second section evaluated the clinical significance of abnormal chloride levels by looking at the development of mortality and other complications in patients who were diagnosed with abnormal chloraemic states, even though the GDG recognized that the development of abnormal chloraemic states may not always have been due solely to the patients' intravenous fluid therapy. The most appropriate design for this section was identified to be cohort or case-control studies in adult, hospitalised patients for areas within the scope of the guideline. A summary of the key characteristics of studies included in this section is presented in Table 17

Table 16: Summary of studies evaluating the development of hyperchloraemia/hyperchloraemic acidosis.

Study	Design	Population	Intervention (Fluids with chloride concentration> 120mmmol/l)	Comparison (Fluids with chloride concentrations < 120mmol/L)	Outcomes
Scheingrabe r et al. 1999[96]	RCT	Patients undergoing major intra-abdominal gynaecologic surgery	Sodium chloride 0.9%	Lactated Ringer's solution	Metabolic acidosis with hyperchloraemia
Shaw et al. 2012[100]	Retrosp ective cohort study	Patients who received iv crystalloids during surgery	Sodium chloride 0.9%	Alternate Balanced Solution	Morbidity and mortality, LOS, electrolyte imbalances
Waters et al. 2001[118]	RCT	Patients undergoing aortic reconstructive surgery	Sodium chloride 0.9%	Lactated ringer's solution	Hyperchloraemia, ICU stay, hospital length of stay, mortality
McFarlane et al. 1994[67]	RCT	Patients scheduled to undergo elective major hepatobiliary or pancreatic surgery	Sodium chloride 0.9%	Alternate Balanced Solution	Chloride levels at end of surgery and 24 hours post- surgery
Takil et al.	RCT	Patients	Sodium chloride	Lactated Ringer's	Chloride levels

Study	Design	Population	Intervention (Fluids with chloride concentration> 120mmmol/l)	Comparison (Fluids with chloride concentrations < 120mmol/L)	Outcomes
2002[106]		undergoing elective major spine surgery	0.9%	solution	intra operatively and up to 12 hours post-operatively
Yunos et al. 2012[126]	Prospective cohort study	Patients admitted to ICU	Chloride liberal fluids: Sodium chloride 0.9%, 4% succinylated gelatine solution, 4% albumin in sodium chloride	Chloride restrictive fluids: Hartmann's solution, Plasma-Lyte 148, 20% albumin solution	AKI, mortality, length of stay in ICU and hospital

Table 17: Summary of studies evaluating the association of hyperchloraemia or hypochloraemia with mortality

Study	Design	Population	Exposure	Non-exposure	Outcomes	Comments
Boniatti et al. 2011[12]	Prospective cohort study	Patients in ICU N=212	Hyperchloraemia	Normo/Hypochloraemia	Mortality, APACHE II score	Evaluates correlation between chloride levels and mortality and morbidity; No mention of what fluids were given
Silva et al. 2009[102]	Prospective cohort study	Patients undergoing surgery and subsequentlly admitted to ICU N=393	Hyperchloraemia at end of surgery	Normochloraemia	Mortality LOS in ICU LOS in hospital	Both groups received Sodium chloride 0.9% but different volumes
Tani et al. 2012[109]	Retrospective cohort study	Critically ill patients in surgical ICU N=488	Hyperchloraemia	Normochloraemia and Hypochloraemia	ICU stay, Hospital stay, ICU mortality %, Hospital mortality%	Evaluates correlation between chloride levels and mortality and length of stay; No mention of what fluids were given

For full details on review protocol, see section C.2.3 in Appendix C.

6.3.3.2 Clinical evidence

We searched for randomised controlled trials and observational studies for both sections of the review.

The GDG identified patients with chronic renal impairment or Acute Kidney Injury (AKI), older people and patients with congestive heart failure as groups who could particularly benefit more from having

serum chloride measured as they may be at higher risk of hyperchloraemia and associated metabolic acidosis or hypochloraemia and alkalosis.

The first part of the review compared patients who received intravenous fluids with chloride concentrations greater than 120mmol/l with those receiving intravenous fluids with chloride concentrations less than 120mmmol/l. Six studies were found. [67,96,100,106,118] Evidence for this section is summarised in the clinical GRADE evidence profile below (see Table 18 and Table 19)

All studies were in patients undergoing surgery. Four studies were RCTs [67,96,106,118] , one was a prospective cohort study [126] and one was a retrospective cohort study.[100]Three studies compared 0.9% sodium chloride solution to lactated Ringer's solution. [96,106,118]Two studies compared 0.9% sodium chloride solution to and alternate balanced solution (as defined in glossary, also see section P.1, Appendix P) .[67,100] One study compared outcomes in patients receiving intravenous fluids based on a chloride restrictive strategy to those in patients on a chloride liberal intravenous strategy.[126]

The second part of the review examined the association between abnormal chloride levels, primarily hyperchloraemia, with mortality and morbidity. Three studies were identified.[12,102,109] These studies compared two groups of patients- one with hyperchloraemia and the other with normochloraemia or hypochloraemia and evaluated the association of chloraemic state with mortality. However, it was unclear whether those patients with hyperchloraemia had developed it as a consequence of intravenous fluid therapy, and the findings from this set of studies were therefore downgraded for indirectness, a decision acknowledged in the section linking evidence to recommendations. The findings from these studies are presented separately (see Table 20). Where the relative or absolute effects were not estimable and other measures of effect were reported in the study, such as co-relation etc., these have been highlighted as not estimable and explained in footnotes.

There were differences between the studies with respect to the rate and volumes of administration of fluids and hence, the total volume of fluid administered differs between studies. This would have had an effect on serum chloride levels and so the results were not pooled across studies.

No evidence was identified in relation to the specific subgroups identified in the review protocol.

See also the study selection flow chart in J.2 (Appendix J), study evidence tables in E.2.1 (Appendix E), and exclusion list in H.2 (Appendix H).

Table 18: Clinical evidence profile: Fluids with chloride concentration less than 120 mmol/L vs Fluids with chloride concentration greater than 120 mmol/L – Dichotomous outcomes

Quality assessment						No of patients		Effect size			
Study id.	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Fluids with chloride <120 mmol/L	Fluids with chloride > 120 mmol/L	Relative effect(Risk ratio (RR) or Odds ratio (OR)	Absolute effect	Quality	Importance
Mortality											
Waters et al. 2001[118]	randomised trial	serious (a, b)	no serious inconsistency	serious indirectness (c)	no serious imprecison	33	33	RR: 1.00(0.07, 15.33)	0 fewer per 1000 (from 28 fewer to 434 more)	LOW	CRITICAL
Shaw et al. 2012[100]	retrospective cohort					926	2778	OR: 0.769(0.484, 1.220)	8 fewer per 1000 (from 17 fewer to 7 more)		
Yunos et al. 2012[126]	prospective cohort					773	760	RR: 0.90(0.70, 1.15)	15 fewer per 1000 (from 44 fewer to 22 more)		
Morbidity (major complication index)											
Shaw et al. 2012[100]	retrospective cohort	serious (b)	no serious inconsistency	serious indirectness (c)	serious imprecison (d)	926	2778	OR: 0.798(0.656, 0.970)	41 fewer per 1000 (from 6 fewer to 72 fewer)	VERY LOW	IMPORTANT
Electrolyte disturbances											
Shaw et al. 2012[100]	retrospective cohort	serious (b)	no serious inconsistency	serious indirectness (c)	serious imprecison (d)	926	2778	OR: 0.753(0.571, 0.994)	24 fewer per 1000 (from 1 fewer to 43 fewer)	VERY LOW	CRITICAL
Renal insufficiency/AKI											
Waters et al. 2001[118]	randomised trial	serious (a, b)	no serious inconsistency	serious indirectness (c)	serious imprecison (d)	33	33	RR: 0.80 (0.24, 2.72)	30 fewer per 1000 (from 115 fewer to 261 more)	VERY LOW	IMPORTANT
Shaw et al. 2012[100]	retrospective cohort					926	2778	OR: 0.451(0.160,	5 fewer per 1000 (from 7 fewer to 2 more)		

Quality assessment						No of patients		Effect size			
Study id.	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Fluids with chloride <120 mmol/L	Fluids with chloride > 120 mmol/L	Relative effect(Risk ratio (RR) or Odds ratio (OR)	Absolute effect	Quality	Importance
								1.273)			
Yunos et al. 2012[126]	prospective cohort					773	760	OR: 0.52 (0.37-0.75)	96 fewer per 1000 (from 47 fewer to 131 fewer)		

(a) In the RCT (Waters et al 2001), allocation concealment was not reported, sample size was too low, and study solutions were not given exclusively;
(b) The observational study (Shaw et al. 2012) was a retrospective database based study which used codes for outcomes which may not be accurate. Also, there were large differences in baseline characteristics between groups.
(c) The studies were conducted in patients undergoing surgery or admitted to ICU which is indirect to the target population; electrolyte disturbances is an indirect outcome as it is not a clinical outcome
(d) Confidence interval(s) crossed MIDs

Table 19: Clinical evidence profile: Fluids with chloride concentration less than 120 mmol/L vs fluids with chloride concentration greater than 120 mmol/L - Continuous outcomes

Quality assessment						No of patients		Effect size		
Study id	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Fluids with chloride <120 mmol/l	Fluids with chloride > 120 mmol/l	Mean Difference	Quality	Importance
Acidosis (reported as pH levels at different time points)-better indicated by higher pH values										
Scheingraber 1999(2 hours)[96]	randomised trials	serious(a)	no serious inconsistency	serious indirectness (b)	no serious imprecision	12	12	not estimable(e)	VERY LOW	CRITICAL
Takil 2002 (2 hours)[106]						15	15	0.09 (0.06, 0.12)		
Takil 2002 (12 hours)[106]						15	15	0.01(-0.01, 0.03)		
Waters 2001 (at admission to surgical ICU after surgery)[118]						33	33	0.05(0.01, 0.09)		
Hyperchloraemia (reported as chloride levels in mEq/L)-better indicated by lower values										
Scheingraber 1999(2 hours)[96]	randomised trials	serious(a)	no serious inconsistency	serious indirectness	no serious imprecision	12	12	not estimable(e)	VERY LOW	CRITICAL

Quality assessment						No of patients				
Study id	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Fluids with chloride <120 mmol/l	Fluids with chloride > 120 mmol/l	Effect size Mean Difference	Quality	Importance
McFarlane1994 (reports increase in Cl-level)(2 hours)[67]				(b)		15	15	-6.3 (-7.61, -4.99)		
Takil 2002(2 hours)[106]						15	15	-5.00(-8.24, -1.76)		
Takil 2002(12 hours)[106]						15	15	-6.00 (-10.35, -1.65)		
Waters 2001(at admission to surgical ICU after surgery)[118]						33	33	-7.00(-9.46, -4.54)		
Length of stay in ICU in hours-better indicated by lower values										
Takil 2002[106]	randomised trials	serious (c)	no serious inconsistency	serious indirectness (d)	no serious imprecision	15	15	5.00(-9.78, 19.78)	VERY LOW	IMPORTANT
Yunos 2002[126]	prospective cohort					773	760	not estimable(e)		
Length of stay in hospital in days-better indicated by lower values										
Takil 2002[106]	randomised trials	serious (c)	no serious inconsistency	serious indirectness (d)	no serious imprecision	15	15	1.00(-0.43, 2.43)	VERY LOW	IMPORTANT
Shaw 2012[100]	Retrospective cohort study					926	2778	0.50 (0.15, 0.85)		
Yunos 2002[126]	prospective cohort					773	760	not estimable(e)		

(a) Method of randomisation and allocation concealment not reported in most studies; details of blinding not reported; studies had very small sample sizes.

(b) Both outcomes are indirect, as pH values and chloride levels are reported instead of well defined clinical outcomes; Also, the measurement of serum chloride levels is done at less than 24 hours in all studies and it is unclear if this is a transient phenomenon and therefore less relevant; Also, the studies were conducted in patients undergoing surgery which is indirect to the target population

(c) One study reported outcomes at less than 24 hours (Takil 2002)and one was a non randomised observational study(Yunos 2012).

(d) The studies were conducted in patients undergoing surgery or admitted to ICU which is indirect to the target population.

(e) No standard deviations reported for pH and chloride levels;

i) Scheingraber 1999- pH in intervention group (Cl-< 120 mmol/L)=7.41 and in control group(Cl->120 mmol/L)=7.28; Chloride level in intervention group(Cl-< 120 mmol/L)= 106mmol/L and in control group (Cl->120 mmol/L)= 115mmol/L.
ii)Yunos 2012- Reported in median and IQR, Length of stay in ICU in hours in intervention group=42.8 hours(IQR, 21.8-90.5) and in control group=42.9hours(21.1-88.6), Length of stay in hospital in days in intervention group=11 days(IQR, 7-22) and control group= 11 days(IQR, 7-21)

Table 20: Clinical evidence profile: Hyperchloraemia vs Normo/Hypochloraemia

Quality assessment						Number of patients		Effect size		Quality	
Study id	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Hyperchloraemia**	**Hypo/normochloraemia**	**Relative effect**	**Absolute effect/Mean difference**		**Important**
Dichotomous outcomes											
Mortality											
Boniatti et al. 2011[12]	prospective cohort study	very serious (a)	no serious inconsistency	very serious indirectness (b)	no serious imprecision	NR	NR	Odds ratio: 1.065 (1.015, 1.118)	not estimable	VERY LOW	CRITICAL
Silva et al. 2009[102]	prospective cohort study					124	269	Risk ratio: 2.60 (1.50, 4.53)	119 more per 1000(from 37 more to 262 more)		
Hospital mortality											
						Hyper	**Normo**			VERY LOW	CRITICAL
Tani et al. 2012[109]	retrospective study	very serious l (a)	no serious inconsistency	very serious indirectness (b)	no serious imprecision	81	364	Risk ratio: 0.96(0.28, 3.27)	2 fewer per 1000(from 28 fewer to 87 more)		
						Hyper	**Hypo**				
Tani et al. 2012[109]	retrospective study	very serious (a)	no serious inconsistency	very serious indirectness (b)	no serious imprecision	81	43	Risk ratio: 0.16(0.05 0.55)	195 fewer per 1000(from 105 fewer to 221 fewer)		
Morbidity- APACHE II score											
Boniatti	prospecti	very	no serious	very serious	not	NR	NR		not	VERY LOW	IMPORTAN

Quality assessment						Number of patients		Effect size		Quality	Important
et al. 2011[12]	ve cohort study	serious (a)	inconsistenc y	indirectness (b)	estimable				estimable(c)		T
Tani et al. 2012[109]	retrospec tive study								not estimable(c)		
Continuous outcomes											
Length of stay in ICU in days- better indicated by lower values											
Silva et al. 2009[102]	prospecti ve cohort study	very serious (a)	no serious inconsistency	very serious indirectnes s (b)	not estimable	124	269		not estimable(d)	VERY LOW	IMPORTAN T
						Hyper	**Normo**				
Tani et al. 2012[109]	retrospec tive study	very serious (a)	no serious inconsistency	very serious indirectnes s (b)	no serious imprecision	81	364		MD: -2.90 (-4.03, -1.77)		
						Hyper	**Hypo**				
Tani et al. 2012[109]	retrospec tive study	very serious (a)	no serious inconsistency	very serious indirectnes s (b)	no serious imprecision	81	43		MD: -9.90(-13.91, -5.89)		
Length of stay in hospital in days- better indicated by lower values											
Silva et al. 2009[102]	prospecti ve cohort study	very serious (a)	no serious inconsistency	very serious indirectnes s (b)	not estimable	124	269		not estimable(d)	VERY LOW	IMPORTAN T
						Hyper	**Normo**				
Tani et al. 2012[109]	retrospec tive study	very serious (a)	no serious inconsistency	very serious indirectnes s (b)	no serious imprecision	81	364		MD: -13.10(-18.72, -7.28)		
						Hyper	**Hypo**				

Quality assessment						Number of patients		Effect size		Quality	Important
Tani et al. 2012[109]	retrospective study	very serious (a)	no serious inconsistency	very serious indirectness (b)	no serious imprecision	81	43		MD: -42.10(-62.19, -22.01)		

(a) Studies were non- randomised observational studies with small sample sizes. The fluid resuscitation strategies prior to and during surgery are not reported; therefore, it is unclear if the effects of hyperchloraemia are due to fluid resuscitation.

(b) The studies are conducted in surgical patients or ITU patients and may not be representative of all patients receiving intravenous fluids, therefore indirect to the target population. It is unclear if all patients received IV fluids and whether the abnormality in chloride levels was a consequence of intravenous fluid therapy, therefore indirect to the intervention.

(c) (c) No raw data or risk ratios reported; In Boniatti et al. 2011- results reported as no correlation between chloride levels and severity of disease according to the APACHE II score; however, in Tani et al. 2012, chloride level was associated with the severity of disease according to APACHE II score- the severity of conditions was greater in hypochloraemic patients in critical care setting.

(d) Mean differences were not estimable as values reported are median and ranges (25^{th} -75^{th} percentiles); In Silva et al. 2009, length of stay in ICU in days was 2.0 (1.0- 3.0) in both groups and length of stay in hospital in days in the group with hyperchloraemia was 13.0(8.0-19.5)and 10.0(6.0-18.0)in group with normo/hypochloraemia.

6.3.3.3 Economic evidence

No relevant economic evaluations for the cost effectiveness of measuring serum chloride concentrations for the purpose of recognising potential problems from hyperchloraemia in people in hospital who require IV fluids were identified.

6.3.3.4 Evidence statements

Clinical

Comparison: Fluids with chloride concentration > 120mmol/L vs. Fluids with chloride concentration< 12ommol/L

Overall, most RCTs and observational studies suggest that the provision of intravenous fluids containing less than 120 mmol/l of chloride is associated with lower mortality and morbidity than the provision of fluids containing more than 120 mmol/l of chloride, although all evidence was very low quality. Individual studies included the following effects:

- One randomised controlled trial with 66 patients and two observational studies with 5237 patients suggested that patients receiving intravenous fluids with chloride concentration less than 120 mmol/l may have less acute injury and lower mortality in comparison to patients receiving intravenous fluids with chloride concentration greater than 120 mmol/l.[Very low quality]
- One observational study with 3704 patients suggested that patients receiving intravenous fluids with chloride concentration less than 120 mmol/l may have less morbidity and less electrolyte disturbances in comparison to patients receiving intravenous fluids with chloride concentration greater than 120 mmol/l.[Very low quality]
- Three randomised controlled trials with 126 patients suggested that that patients receiving intravenous fluids with chloride concentration less than 120 mmol/l may have less acidosis and less hyperchloremia compared to patients receiving intravenous fluids with chloride concentration greater than 120 mmol/l. [Very low quality]
- One randomised controlled trial with 30 patients suggested that patients receiving intravenous fluids with chloride concentration greater than 120 mmol/l for intravenous fluid therapy may have shorter length of stay in ICU as compared to patients receiving intravenous fluids with chloride concentration less than 120 mmol/l but the study was very small with wide variation in ICU lengths of stay and consequently extremely wide confidence intervals which did not allow any real conclusions to be drawn. [Very low quality]
- One randomised controlled trial with 30 patients and one observational study with 3704 patients suggested that patients receiving intravenous fluids with chloride concentration greater than 120 mmol/l for intravenous fluid therapy may have shorter length of stay in hospital as compared to patients receiving intravenous fluids with chloride concentration less than 120 mmol/l. [Very low quality]

Comparison: Hyperchloraemia vs Normo/Hypochloraemia

Overall, the associations between serum chloride level and clinical outcomes were difficult to interpret, with some studies suggesting worse clinical outcomes with hyperchloraemia compared to normal or low chloride levels, whereas others suggested that the worst outcomes were in patients who were hypochloraemic. Furthermore, it was not possible to determine whether abnormal serum chloride in either direction was predominantly a reflection of inappropriate IV fluid prescribing rather than underlying disease states. Individual studies included the following effects:

- Two prospective cohort studies with 602 patients suggested that patients with hyperchloraemia have a higher risk of mortality compared to patients with normo/hypo-chloraemia, and chloride level was independently associated with mortality in a multiple regression model. However, evidence from another retrospective cohort study with 488 patients suggested that patients with hypochloraemia had the greatest hospital mortality followed by patients with normochloraemia and then followed by patients with hyperchloraemia. [Very low quality]
- One prospective cohort study with 212 patients suggested that there was no correlation between chloride level and the severity of disease according to the APACHE II score. However, another retrospective cohort study with 488 patients suggested that chloride level was associated with the severity of disease and the severity of disease was highest in patients with hypochloraemia. [Very low quality]
- One prospective cohort study with 393 patients showed that there was no difference in length of stay in ICU between patients with hyperchloraemia as compared to those with hypo/normochloraemia. However, one retrospective cohort study with 488 patients suggested that patients with hypochloraemia had the greatest length of stay in hospital and ICU followed by patients with normochloraemia and then followed by patients with hyperchloraemia. [Very low quality]

Economic

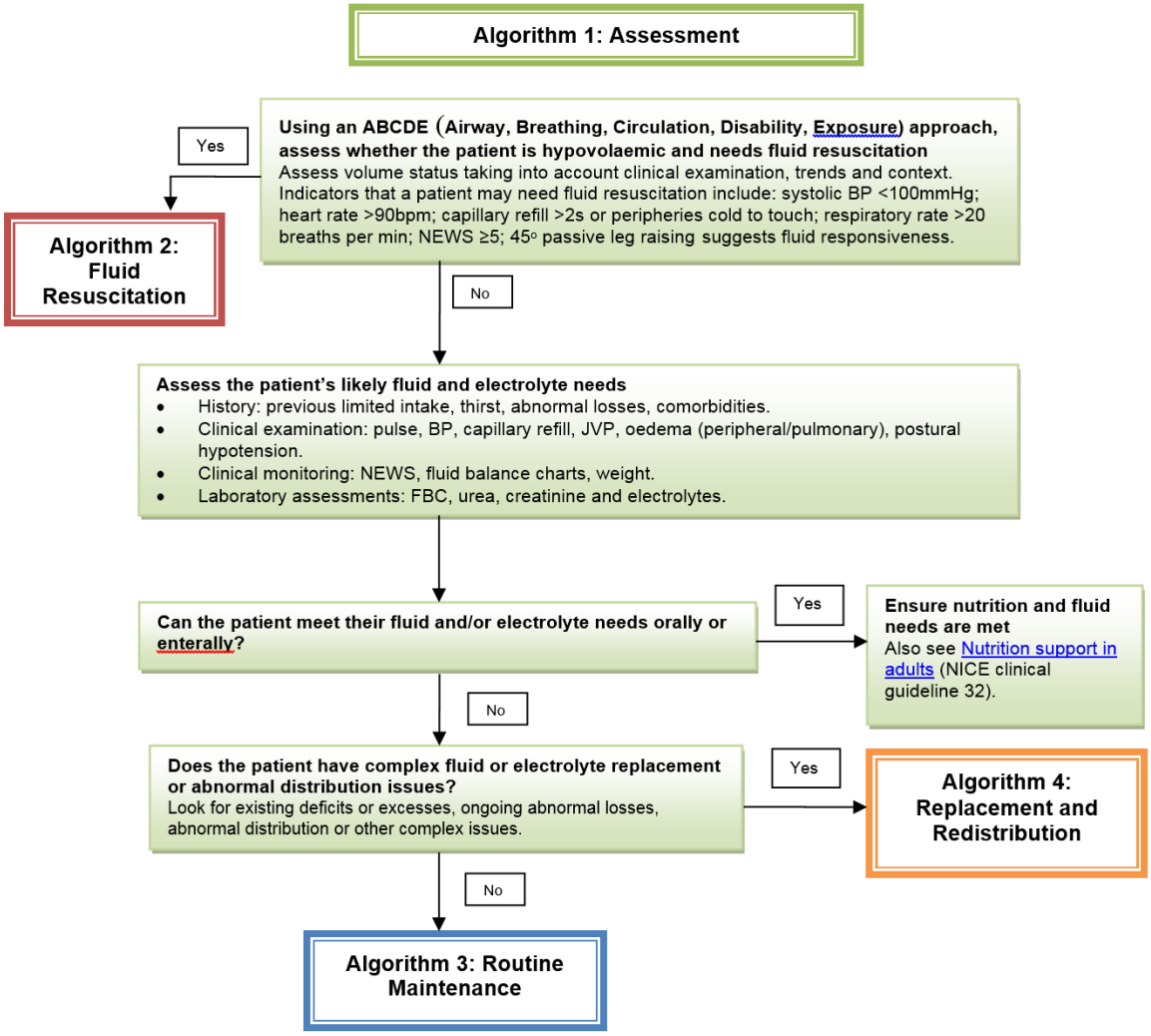
- No relevant economic evaluations were identified.

6.3.3.5 Recommendations and link to evidence

Recommendations	**15. If patients have received IV fluids containing chloride concentrations greater than 120 mmol/l (for example, sodium chloride 0.9%), monitor their serum chloride concentration daily. If patients develop hyperchloraemia or acidaemia, reassess their IV fluid prescription and assess their acid–base status. Consider less frequent monitoring for patients who are stable.**
Relative values of different outcomes	The most important outcomes were agreed by the GDG as the development of sustained hyperchloraemia and hyperchloraemic acidosis which are likely to be direct consequences of receiving intravenous fluids with high concentrations of serum chloride. Mortality and morbidity were also considered important outcomes. The presence of hypochloraemia is also important but is often caused by underlying disease states with high chloride losses or excess water retention rather than by inappropriate IV fluid prescribing alone.
Trade-off between clinical benefits and harms	Measurement of serum chloride concentration helps in the early identification of hyperchloraemia, hyperchloraemic acidosis and hypochloraemia which could be significant in decreasing associated morbidity and mortality. Although the wider use of chloride measurement would increase the rate of invasive monitoring if no other tests were being undertaken, it is very unlikely that this would ever occur in reality since patients receiving IV fluids also require other laboratory monitoring.
Economic considerations	No evidence of cost-effectiveness was found. Some analysers will routinely measure serum chloride concentration, even if the test result is not revealed to the ordering clinician unless specifically requested. In this case there will be no incremental cost associated with ordering the test. In other hospitals, however, there will be an increased cost associated with introducing wider chloride measurement although this should not amount to more than a few pence per test. The GDG expects this modest increase in cost to be offset by cost savings from averting complications in addition to associated improvements in health outcome.
Quality of evidence	Overall, most RCTs and observational studies suggest that the provision of

	intravenous fluids containing <120 mmol/l is associated with lower mortality and morbidity than the provision of fluids containing >120 mmol/l. Four RCTs and one observational study contributed to the evidence which was of very low quality. Overall, the associations between chloraemic state and clinical outcomes were very difficult to interpret, with some studies suggesting worse clinical outcomes with hyperchloraemia compared to normal or low chloride levels, whereas others suggested that the worst outcomes were in patients who were hypochloraemic. Evidence was derived from three cohort studies and was of very low quality and furthermore, it was not possible to determine whether abnormal serum chloride level either high or low was predominantly a reflection of inappropriate IV fluid prescribing rather than underlying disease states.
Other considerations	The review question was addressed in two sections. The first section evaluated the development of hyperchloraemia in patients receiving iv fluids with chloride concentrations greater than 120mmmol/l. However, all the studies reported outcomes at less than 24 hours after infusion and it was unclear if the hyperchloraemia was sustained beyond this and was relevant. The second section presented evidence from studies which evaluated association of abnormal chloride levels with mortality and morbidity. A major drawback of this evidence is that it was unclear if the patients had received intravenous fluids in the studies and the hyperchloraemia was a consequence of this. The evidence has been downgraded for indirectness on this account and the GDG agreed that it overall, the findings could not actually contribute to decision making. The lack of high quality evidence demonstrating an association between serum chloride and clinical outcomes was acknowledged by the GDG and therefore recommendations were based on the evidence reviewed and the consensus expert opinion of the GDG members. The GDG also discussed the importance of linking this recommendation with training and education about how to interpret serum chloride level and how to use it as an assessment tool rather than to simply change the IV fluid prescribed as a result of a single serum chloride measurement.

6.3.4 Algorithm 1: Assessment


Algorithm 1: Assessment
Using an ABCDE (Airway, Breathing, Circulation, Disability, Exposure) approach, assess whether the patient is hypovolaemic and needs fluid resuscitation
Assess volume status taking into account clinical examination, trends and context. Indicators that a patient may need fluid resuscitation include: systolic BP <100mmHg; heart rate >90bpm; capillary refill >2s or peripheries cold to touch; respiratory rate >20 breaths per min; NEWS ≥5; 45° passive leg raising suggests fluid responsiveness.
Yes
Algorithm 2: Fluid Resuscitation
No
Assess the patient's likely fluid and electrolyte needs
History: previous limited intake, thirst, abnormal losses, comorbidities.
Clinical examination: pulse, BP, capillary refill, JVP, oedema (peripheral/pulmonary), postural hypotension.
Clinical monitoring: NEWS, fluid balance charts, weight.
Laboratory assessments: FBC, urea, creatinine and electrolytes.
Can the patient meet their fluid and/or electrolyte needs orally or enterally?
Yes
Ensure nutrition and fluid needs are met
Also see Nutrition support in adults (NICE clinical guideline 32).
No
Does the patient have complex fluid or electrolyte replacement or abnormal distribution issues?
Look for existing deficits or excesses, ongoing abnormal losses, abnormal distribution or other complex issues.
Yes
Algorithm 4: Replacement and Redistribution
No
Algorithm 3: Routine Maintenance

This section links the evidence to Algorithm 1 and recommendation bullet specific to assessment.

Recommendations	**Offer IV fluid therapy as part of a protocol (see Algorithms for IV fluid therapy):** • **Assess patients' fluid and electrolyte needs following Algorithm 1: Assessment.** • **If patients need IV fluids for fluid resuscitation, follow Algorithm 2: Fluid resuscitation.** • **If patients need IV fluids for routine maintenance, follow Algorithm 3: Routine maintenance.** • **If patients need IV fluids to address existing deficits or excesses, ongoing abnormal losses or abnormal distribution, follow Algorithm 4: Replacement and redistribution.**
Relative values of different outcomes	The GDG were interested in all cause mortality, length of hospital stay, complications including renal and respiratory problems, and morbidity as measured by SOFA or MODS scores.
Trade-off between clinical benefits and harms	Protocols are by design created to support clinical decision making, and are not meant to replace clinical judgement at the bedside.

Economic considerations	In chapter 1 it was noted that for patients with sepsis, protocolised care was found to be cost-effective for sepsis patients in two studies and cost saving in a third study. This evidence was considered to be partially applicable and with potentially serious limitations. There was no cost-effectiveness evidence for patients without sepsis. However, given that the health improvements observed in the review of clinical effectiveness evidence were just as pronounced for intra-operative care the GDG felt that the economic benefits of protocols are very likely to be achievable across all settings.
Quality of evidence	The algorithm was based on established guidance (NEWS, Advanced Life Support guidance, NICE CG50), consensus opinion of the GDG members and findings from the systematic review on clinical effectiveness of protocolised care. Quality of evidence for outcomes analysed in the systematic review was very low. For details on quality of evidence for individual reviews, clinical evidence profiles in sections.
Other considerations	Despite the paucity of evidence on the use of protocols for IV fluid administration, the GDG felt that protocolised care in general achieves better outcomes for patients and therefore decided that an algorithmic approach to assessment of fluid and electrolyte status is appropriate in this context. In designing the algorithm, the GDG placed particular emphasis on developing recommendations that a foundation year doctor could follow. The GDG agreed that recognition of the seriously ill patient with a NEWS score of 5 or more should prompt seeking of expert help, alongside the initiation of resuscitation. The GDG consensus on 'expert help' is defined by NICE CG50. This recommendation was identified as a key priority for implementation by the GDG.

6.4 Research recommendations

1. What is the incidence of complications during, and as a consequence of, IV fluid therapy?

Why this is important

This is almost certainly under-reported in the ward setting with significant implications for patients, predominantly morbidity through to mortality. It is probable that complications of fluid therapy are frequent and may be associated with increased clinical needs, such as critical care and, on occasion, may necessitate resuscitation. Lack of a set of clearly defined features of the complications of fluid mismanagement compounds the problem. It is important to define these features and then undertake an observational study in a hospital setting to determine the epidemiology of these complications. Such a study would highlight the prevalence of fluid related complications and inform the development of preventive measures.

7 Intravenous fluid therapy for fluid resuscitation

7.1 Introduction

Urgent fluid resuscitation is needed if a patient has lost enough fluid either acutely or chronically to start showing signs of decompensation. Sympathetic responses attempt to compensate for the decrease in intravascular volume by prioritising blood flow to vital organs. The heart rate is usually increased (tachycardia) and peripheral vasoconstriction increases diastolic blood pressure. and the total effective intravascular volume is reduced by vasoconstriction. The tachycardia and reduced peripheral perfusion is followed by a marked decrease in systolic blood pressure when more than 30-40% of the intravascular volume has been lost. The changes are therefore manifest by tachycardia and reduced peripheral perfusion and as the volume deficit increases, an increasingly marked fall in blood pressure with dysfunction of most organ systems. Central nervous system depression causes agitation, confusion or decreased level of consciousness, renal hypo-perfusion causes oliguria and general tissue hypo-perfusion causes acidosis, often with compensatory tachypnoea.

Shock is defined as ‘a life threatening condition with generalized maldistribution of blood flow causing failure to deliver and/or utilize adequate amounts of oxygen, leading to tissue dysoxia. ’. It is always better to prevent shock and prevent any signs of end organ failure.

The presence of two or more of the following is likely to indicate shock.

•Pulse rate > 20 bpm above baseline

•Systolic BP 20 mmHg less than normal

•Capillary refill greater than 2 seconds

•Respiratory rate > 20 per minute

•Urine output less than 0.3 ml/kg/h

The presence of organ dysfunction is also suggested by metabolic acidosis, increased plasma lactate values and a central venous oxygen saturation of <70%.

There is a wide range in the ability of patients to compensate for fluid loss. Patients with significant co-morbidities and those taking cardiovascular drugs, for example, may decompensate with relatively little fluid loss. Young, very fit patients will compensate for much greater loss of intravascular volume and their systolic blood pressure may be preserved until severe shock has ensued.

In the UK, the recent adoption of the National Early Warning Score (NEWS) provides a basic universal method to identify the signs of physiological decompensation.[95] NEWS is derived from six physiological parameters: respiratory rate, arterial blood oxygen saturation, temperature, systolic blood pressure, pulse rate and level of consciousness; an adjustment is made for patients receiving oxygen therapy. The aggregate score triggers a response from nursing and/or medical staff depending on the thresholds set by local policy.

Treatment of shock requires urgent intravenous fluid infusion to restore intravascular volume, reverse decompensation and restore organ perfusion. Other immediate measures may also be needed, including high-flow oxygen, leg raising/head down tilt, the use of inotropes and specific measures to treat the original cause of hypovolaemia, but these are beyond the scope of this guidance.

Although it is critical that adequate fluid is given to restore and then maintain intravascular volume, it is important to avoid fluid and/or electrolyte overload. Modifying and monitoring the intravascular volume is relatively easy but this is much more difficult for the interstitial and intracellular fluid compartments. The amount of fluid needed for resuscitation is extremely variable and so frequent reassessment is needed. The literature review aims to establish the best type of fluid(s) for resuscitation and the optimum timing and volume of administration.

7.1.1 IV Fluids for resuscitation

A variety of crystalloids, artificial colloids and human albumin solutions have been used for fluid resuscitation and there has been considerable debate for more than 30 years about the best type of fluid to use and the optimal volume and rates of delivery. Solutions such as glucose 5% and glucose saline are not suitable for fluid resuscitation because they lead to rapid dilution of plasma sodium and only modest increases in circulatory volume because of their tendency to distribute rapidly across all fluid compartments.

There has been considerable debate over 30 years or more in relation to the best type of fluid to use for fluid resuscitation, as well as the optimal volume and rate of delivery. These debates have revolved around the following:

- Synthetic colloids as well as albumin solutions have theoretical advantages over crystalloids in terms of their ability to expand intravascular volume rather than the interstitial space but in recent years it has become clear that they are less effective in terms of intravascular volume expansion and retention than originally thought, especially in pathophysiological states when, in the presence of hypovolaemia and high capillary escape rates, all IV fluids have very different post-infusion distributions than in health. Colloids are also more expensive than crystalloids.
- The synthetic colloids available vary considerably in size and structure and therefore have different distributions and capacity to expand plasma volume, as well as other differing properties including half-life and potential toxicity. High (450 kD) and medium molecular weight (200 kD) hydroxyethyl starches have also been shown to have adverse effects and as a result are now rarely used in the UK, especially in admission units or general ward settings. For this reason, the high and medium molecular weight starches were not included in our review.
- Balanced solutions, either balanced crystalloids per se or colloids made up in a balanced crystalloid base, have theoretical advantages over sodium chloride 0.9% or colloids made up in sodium chloride 0.9% since infusion of more sodium may lead to increased post-resuscitation interstitial sodium and water retention and infusion of more chloride might cause hyperchloraemia with possible associated adverse effects such as acidosis and decreases in renal perfusion and glomerular filtration. [18,79]

Despite the years of debate, uncertainty remains about the best fluid to use and many decisions are actually based on personal preferences.

The intention of this chapter is to examine the evidence available on IV fluid therapy for fluid resuscitation. This evidence will inform basic guidance on when to use IV fluid resuscitation, as well as the type, volume and rate of infusion of fluid. The guidance applies to hospital patients in admission and general ward areas being treated by healthcare professionals who are not experts in fluid resuscitation.

7.2 Intravenous fluid therapy for fluid resuscitation- Types of fluid

The objective of the formal clinical evidence review was to identify the most clinically and cost effective types of fluid to be used for resuscitation in general hospital admission units and ward settings.

Review question: What is the most clinical and cost effective intravenous fluid for resuscitation of hospitalised patients?

We searched for randomised controlled trials (RCT) comparing the effectiveness for improving outcomes of gelatin, hydroxyethylstarch (tetrastarch), sodium chloride 0.9% solution, balanced solutions (Ringer's lactate/acetate, Hartmann's solution) and albumin (all compared to each other) as interventions in hospital patients requiring IV fluid resuscitation.

The guidance contained in this document is focussed on prescribing IV fluids in hospital admission units and general wards, therefore, the evidence review did not include large penta- or hexa-starches nor hyper-oncotic crystalloids or colloids as comparators because these fluid types are rarely if ever used in such settings.

Review strategy:

The target population for this review was adults in hospital who were receiving intravenous fluid therapy for fluid resuscitation. The GDG discussed and agreed that if no evidence in the target population was identified, the review would include indirect evidence in the following order:

1.patients in intensive care units/ high dependency units,

2.emergency services, including patients fluid resuscitation in ambulances and emergency services

3.intra-operative patients (this would however exclude patients receiving IV fluids for normovolaemic hemodilution, intraoperative cardiac bypass surgery and preload for spinal anaesthesia as these were deemed to be too indirect or relevant to the target population)

For more details on the review protocol, see section C.3.1, Appendix C.

One Cochrane review was identified comparing crystalloids with colloids in critically ill patients[83]. Although this was partially relevant to our review question, it was not included as the protocol for this review differed from that of the Cochrane review in the following respects:

- The Cochrane review[83] included studies on patients with burns and traumatic brain injury that were out of the scope of this guideline.
- The Cochrane review included pentastarches, hexastarches and hyper-oncotic crystalloids and colloids.
- The Cochrane review included studies conducted before 1990 whilst the GDG felt that that since practice in fluid resuscitation has evolved over time, studies prior to 1990 may not be relevant and they were therefore excluded.

A number of other Cochrane reviews were also identified which evaluated some of the interventions included in this review. [13,23,26,51,66,88,111] These were even less relevant to the review protocol and therefore not included. For reasons of exclusion, see the excluded studies list in section H.2, Appendix H).

Below is a matrix showing where evidence was identified. A box filled with a number represents the number of studies found for that comparison and subsequently reviewed in this chapter. There is no discussion in the chapter on comparisons where no studies were identified.

Table 21: Matrix of treatment comparisons

	Gelatin	Sodium chloride 0.9%	Balanced solutions	Albumin
Tetrastarch	5	4	1	0

	Gelatin	Sodium chloride 0.9%	Balanced solutions	Albumin
Gelatin		1	3	0
Sodium chloride 0.9%			0	1
Balanced solutions				0
Albumin				

The number in each box indicates the number of studies identified for that comparison.

7.2.1 Gelatin

Comparisons: Gelatin vs hydroxyethylstarch, sodium chloride 0.9%, balanced solutions (Ringer's lactate/ acetate, Hartmann's solution) and albumin.

7.2.1.1 Clinical evidence

Seven RCTs were identified as relevant to this review question.[33,34,41,45,64,113,125]

- Five RCTs compared Gelatin with tetrastarches [33,34,45,64,113,125]
- Three RCTs compared Gelatin with lactated Ringer's solution[34,41,125]
- One RCT compared Gelatin with sodium chloride 0.9% solution[113]
- Of the six studies comparing gelatin to tetrastarches, three were three-armed trials with physiological lactated solutions as the third comparator. [34,45,125] One further trial was also three-armed with sodium chloride 0.9% as the additional comparator.[113]

The populations included in the studies varied:

- One was on patients undergoing gastrectomy [45].
- One included patients undergoing orthopaedic surgery [41],
- Two were on people who had open aortic aneurysm surgery [33,64]
- Two were on postoperative patients; one study had a population of hypovolaemic postoperative patients [34] and one study had a population of postoperative cardiac and vascular surgery patients [113]
- One was on trauma patients[125]

There was heterogeneity in the interventions of the included studies:

- The intervention fluid administered to the study groups was fixed (either by volume of fluid, or by protocol of fluid administration) in 5 studies [33,34,45,113,125], and was varied according to which fluid was received in one studies [41]Two studies did not report the protocol for fluid administration.[64,125]

Some studies reported median values for the outcomes 'amount of study fluid received' [113], length of stay in ICU [33,34] and 'length of stay in hospital' [33]; these outcomes could not be meta-analysed.

The findings are summarised in the clinical GRADE evidence profile below (see Table 22, Table 23 and Table 24). See also the full study evidence tables in section E.3.1, Appendix E and forest plots in section G.3.1, Appendix G. For details on excluded studies, see section H.2, Appendix H.

Table 22: Clinical evidence profile: Gelatin vs tetrastarch

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	GELATIN	HES	Relative (95% CI)	Absolute	Quality	Importance
Mortality[33,34,64,113]												
4	randomised trials	Serious(a)	Serious(b)	very serious(c)	no serious imprecision	none	21/119 (17.6%)	17/120 (14.2%)	RR 1.24 (0.70 to 2.18)	34 more per 1000 (from 43 fewer to 167 more)	VERY LOW	CRITICAL
Mortality – Postoperative[34,113]												
2	randomised trials	Serious(a)	no serious inconsistency	very serious(c)	no serious imprecision	none	13/66 (19.7%)	14/67 (20.9%)	RR 0.93 (0.49 to 1.78)	15 fewer per 1000 (from 107 fewer to 163 more)	VERY LOW	CRITICAL
Mortality - Aortic aneurysm [33,64]												
2	randomised trials	Serious(a)	no serious inconsistency	very serious(c)	no serious imprecision	none	8/53 (15.1%)	3/53 (5.7%)	RR 2.70 (0.76 to 9.56)	96 more per 1000 (from 14 fewer to 485 more)	VERY LOW	CRITICAL
Volume of study fluid administered (Better indicated by lower values)[33,41,45,64]												
4	randomised trials	Serious(d)	no serious inconsistency	Serious(e)	very serious(f)	none	85	85	-	MD 103.28 higher (96.10 lower to 302.67 higher)	VERY LOW	IMPORTANT
Volume of study fluid administered - Intraoperative (Better indicated by lower values)[41,45]												
2	randomised trials	Serious(d)	no serious inconsistency	Serious(e)	very serious(f)	none	32	32	-	MD 120.16 higher (95.3 lower to 335.61 higher)	VERY LOW	IMPORTANT
Volume of study fluid administered - Aortic aneurysm (Better indicated by lower values) [33,64]												
2	randomised trials	Serious(d)	no serious inconsistency	Serious(e)	very serious(f)	none	53	53	-	MD 2.66 higher (523.46 lower to 528.77 higher)	VERY LOW	IMPORTANT
Total volume of fluid administered (Better indicated by lower values)[41]												
1	randomised trials	Serious(g)	no serious inconsistency	Serious(h)	very serious(f)	none	20	20	-	MD 193 higher (99.23 lower to 485.23 higher)	VERY LOW	IMPORTANT

(a)Allocation concealment not reported in one study (Gondos 2010); relevant baseline criteria not reported in most of the studies
(b) I2 value 70.9%

(c)One study was conducted in post-operative patients who may already have been haemodynamically stable (Gondos 2010) and two studies were in patients with abdominal aortic aneurysm surgery which was agreed to be a highly indirect population (Godet 2008, Mahmood 2009)
(d) Relevant baseline characteristics not reported in most of the studies; allocation concealment not reported in 2 studies(Innerhofer 2002, Jin 2001); details of blinding not reported in two studies(Godet 2008, Mahmood 2009)
(e) Two studies were conducted in intraoperative patients (Innerhofer 2002, Jin 2001) and two studies in patients undergoing abdominal aortic aneurysm surgery(Godet 2008, Mahmood 2009) and findings may not be generalisable to all patients receiving fluid resuscitation
(f) Confidence interval crosses both MIDs
(g) Relavant baseline characteristics not reported; details of allocation concealment not reported
(h) Study conducted in intraoperative patients and findings may not be generalisable to all patients receiving fluid resuscitation (Innnerhofer 2002)

Table 23: Clinical evidence profile: Gelatin vs lactated Ringer's solution

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**GELATIN**	**RINGER'S LACTATE**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Mortality[34,125]												
2	randomised trials	Serious (a)	no serious inconsistency	Serious(b)	no serious imprecision	none	14/68 (20.6%)	18/66 (27.3%)	RR 0.76 (0.42 to 1.4)	65 fewer per 1000 (from 158 fewer to 109 more)	LOW	CRITICAL
Mortality – Trauma[125]												
1	randomised trials	Serious (a)	no serious inconsistency	Serious(b)	no serious imprecision	none	2/18 (11.1%)	3/16 (18.8%)	RR 0.59 (0.11 to 3.11)	77 fewer per 1000 (from 167 fewer to 396 more)	LOW	CRITICAL
Mortality – Postoperative[34]												
1	randomised trials	Serious (a)	no serious inconsistency	Serious(b)	no serious imprecision	none	12/50 (24%)	15/50 (30%)	RR 0.8 (0.42 to 1.53)	60 fewer per 1000 (from 174 fewer to 159 more)	LOW	CRITICAL
Volume of study fluid administered (Better indicated by lower values)[41,45]												
2	randomised trials	very serious (c)	no serious inconsistency	Serious(d)	no serious imprecision	none	32	32	-	SMD 3.58 lower (4.41 to 2.76 lower)	VERY LOW	IMPORTANT
Total volume of fluid administered (Better indicated by lower values)[41]												
1	randomised trials	very serious	no serious inconsistency	Serious(d)	no serious imprecision	none	20	20	-	MD 1396 lower (1986.95 to 805.05 lower)	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	GELATIN	RINGER'S LACTATE	Relative (95% CI)	Absolute	Quality	Importance
		(c)										

(a) Relevant baseline characteristics not reported in both studies; details of allocation concealment not reported in both studies(Wu 2001, Gondos 2010); details of randomisation not reported in one study(Wu 2001)
(b)One study was in post-operative pateints who may already have been haemodynamically stable (Gondos 2010) and the other study was in trauma patients (Wu 2001);findings from both may not be generalisable to all patients receiving fluid resuscitation
(c) Relevant baseline characteristics not reported; details of allocation concealment not reported and bliniding of participants and investigators was unclear.
(d)Study conducted in intraoperative patients and findings may not be generalisable to all pateints receiving fluid resuscitation

Table 24: Clinical evidence profile: Gelatin vs. Sodium chloride 0.9%

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Gelatin	Sodium chloride 0.9%	Relative (95% CI)	Absolute	Quality	Importance
Mortality[113]												
1	randomised trials	Serious (a)	no serious inconsistency	very serious(b)	no serious imprecision	none	1/16 (6.3%)	1/16 (6.3%)	RR 1 (0.07 to 14.64)	0 fewer per 1000 (from 58 fewer to 853 more)	VERY LOW	CRITICAL

(a)Details of allocation concealment not reported; no information provided on fluid composition
(b) Study conducted in post-operative cardiac and vascular surgery patients and findings may not be generalisable to all patients receiving fluid resuscitation (Verheij 2006)

7.2.1.2 Economic evidence

No economic studies were identified on the cost-effectiveness of gelatin vs. hydroxyethylstarch for intravenous fluid resuscitation of hospitalised patients.

An original cost analysis was developed to compare gelatin, hydroxyethylstarch (tetrastarch), albumin and crystalloids - see section 7.2.3.2

7.2.1.3 Evidence statements

Clinical

Gelatin vs tetrastarch

The review of the use of gelatin compared with tetrastarch for fluid resuscitation showed no consistent advantage or disadvantage with the use of gelatin in terms of mortality or the volume of fluid that needed to be infused.

There was also no clear evidence that the use of gelatin for fluid resuscitation granted any significant advantage or disadvantage over the use of either Ringer's lactate or 0.9% sodium chloride in terms of mortality.

No studies reported morbidity, respiratory complications, renal complications or length of stay in hospital or ICU.

Outcome: Mortality

Four studies with 239 patients from a mixed population (post-operative patients, aortic aneurysm surgery) suggested that there may be no difference in mortality between patients receiving gelatin or tetrastarch for fluid resuscitation. Of these, two studies with post-operative patients showed no difference in mortality between patients receiving gelatin or tetrastarch. Two studies with 106 patients who had undergone surgery for aortic aneurysm suggested lower mortality with tetrastarch than gelatin but there was some uncertainty. All the evidence was of very low quality.

Outcome: Volume of study fluid received

Four studies with 170 patients from a mixed population (intraoperative, aortic aneurysm surgery) suggested that patients receiving tetrastarch required lower volumes of fluid for resuscitation. This effect was independently observed in two studies with 64 intraoperative patients but there was considerable uncertainty. Two studies in 106 aortic aneurysm surgery patients suggested no difference in volumes of fluid required for fluid resuscitation, but there was considerable uncertainty. All of the evidence was of very low quality.

Gelatin vs balanced crystalloid solutions

Outcome: Mortality

Two studies with 134 patients from mixed populations (trauma, postoperative) suggested that there was no difference in mortality between patients receiving gelatin or lactated Ringer's solution for fluid resuscitation, but there was considerable uncertainty. This effect was also observed independently in both trauma and post-operative patients, but there was considerable uncertainty. The evidence was of very low quality.

Outcome: Volume of study fluid received

Two studies with 64 intraoperative patients showed that patients receiving gelatin required lower volumes for fluid resuscitation compared to those receiving lactated Ringer's solution. The evidence was of very low quality.

Gelatin vs sodium chloride 0.9%

One study with 32 patients suggested that there was no difference in mortality between patients receiving gelatin or sodium chloride 0.9% for fluid resuscitation, but there was considerable uncertainty. The evidence was of very low quality.

Economic

7.2.1.4 See 7.2.3.3

7.2.1.5 Recommendations and link to evidence

See recommendations and link to evidence in section7.4

7.2.2 Tetrastarch

7.2.2.1 Clinical evidence

Five RCTs were identified relevant to this review question.[25,38,43,70,84] Three studies were in sepsis patients, [25,38,84] one was in critically injured patients[43] and one study was conducted in all patients admitted to intensive care units and included those with sepsis and trauma.[70]

The GDG prioritised evaluation of the effects of tetrastarches for the purposes of this review as these were considered to be most widely used in admission and general ward settings. Four of the studies compared 6% hydroxyethylstarch 130/0.4 to sodium chloride 0.9% [25,38,43,70] and one study compared 6% hydroxyethylstarch 130/0.42 to Ringer's acetate solution[84].

The outcomes reported across studies included mortality at 30 and 90 days, SOFA scores, renal outcomes, and length of stay in hospital and intensive care units. No studies reported any quality of life outcomes.

The evidence is summarised in the clinical GRADE evidence profile below (see Table 25 and Table 26)

See also the flow diagram for study selection in section J.3, Appendix J, evidence tables in section E.3.2, Appendix E, forest plots in section G.3.2 in Appendix G and excluded studies list in section H.3, Appendix H.

Table 25: Clinical evidence profile: Tetrastarch compared to Sodium chloride 0.9% for fluid resuscitation

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Tetrastarch**	**Sodium Chloride 0.9%**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
All cause mortality (90 days)[38,70]												
2	randomised trials	no serious risk of bias	no serious inconsistency	Serious(a)	no serious imprecision	none	637/3414 (18.7%)	598/3431 (17.4%)	RR 1.07 (0.97 to 1.18)	12 more per 1000 (from 5 fewer to 31 more)	MODERATE	CRITICAL
All cause mortality (30 days)[38,43,70]												
3	randomised trials	no serious risk of bias	no serious inconsistency	Serious(a)	no serious imprecision	none	501/3469 (14.4%)	467/3479 (13.4%)	RR 1.07 (0.96 to 1.21)	9 more per 1000 (from 5 fewer to 28 more)	MODERATE	CRITICAL
All cause mortality (30 days) – Trauma[43]												
1	randomised trials	Serious(b)	no serious inconsistency	no serious indirectness	no serious imprecision	none	12/56 (21.4%)	6/53 (11.3%)	RR 1.89 (0.77 to 4.68)	101 more per 1000 (from 26 fewer to 417 more)	MODERATE	CRITICAL
All cause mortality (30 days) – Sepsis [38,70]												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	489/3413 (14.3%)	461/3426 (13.5%)	RR 1.06 (0.94 to 1.2)	8 more per 1000 (from 8 fewer to 27 more)	HIGH	CRITICAL
Length of stay in ICU (Better indicated by lower values)[38,70]												
2	randomised trials	no serious risk of bias	Serious(c)	Serious(a)1	very serious(d)	none	3441	3465	-	MD 1.51 lower (6.43 lower to 3.4 higher)	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Tetrastarch	Sodium Chloride 0.9%	Relative (95% CI)	Absolute		
Length of stay in hospital (Better indicated by lower values) [38,70]												
2	randomised trials	no serious risk of bias	no serious inconsistency	Serious(a)	no serious imprecision	none	3441	3465	-	MD 0.2 higher (0.19 to 0.21 higher)	MODERATE	IMPORTANT
New organ failure (Cardiovascular- SOFA score≥3)[70]												
1	randomised trials	no serious risk of bias	no serious inconsistency	Serious(a)	no serious imprecision	none	663/1815 (36.5%)	722/1808 (39.9%)	RR 0.91 (0.84 to 0.99)	36 fewer per 1000 (from 4 fewer to 64 fewer)	MODERATE	IMPORTANT
New organ failure(Respiratory)[70]												
1	randomised trials	no serious risk of bias	no serious inconsistency	Serious(a)	no serious imprecision	none	540/2062 (26.2%)	524/2094 (25%)	RR 1.05 (0.94 to 1.16)	13 more per 1000 (from 15 fewer to 40 more)	MODERATE	IMPORTANT
AKI- RIFLE- Risk[43,70]												
2	randomised trials	no serious risk of bias	no serious inconsistency	Serious(a)	no serious imprecision	none	1796/3365 (53.4%)	1924/3389 (56.8%)	RR 0.94 (0.9 to 0.98)	34 fewer per 1000 (from 11 fewer to 57 fewer)	MODERATE	IMPORTANT
AKI- RIFLE- Risk – Trauma (subgroup)[43]												
1	randomised trials	Serious(b)	no serious inconsistency	no serious indirectness	very serious(d)	none	8/56 (14.3%)	12/54 (22.2%)	RR 0.64 (0.29 to 1.45)	80 fewer per 1000 (from 158 fewer to 100 more)	VERY LOW	IMPORTANT
AKI- RIFLE- Risk – Sepsis (subgroup)[70]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1788/3309 (54%)	1912/3335 (57.3%)	RR 0.94 (0.9 to 0.98)	34 fewer per 1000 (from 11 fewer to 57 fewer)	HIGH	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Tetrastarch**	**Sodium Chloride 0.9%**	**Relative (95% CI)**	**Absolute**		
AKI- RIFLE-Injury [43,70]												
2	randomised trials	no serious risk of bias	no serious inconsistency	Serious(a)	no serious imprecision	none	1134/3321 (34.1%)	1261/3354 (37.6%)	RR 0.91 (0.85 to 0.97)	34 fewer per 1000 (from 11 fewer to 56 fewer)	MODERATE	IMPORTANT
AKI- RIFLE-Injury – Trauma (subgroup) [43]												
1	randomised trials	Serious(b)	no serious inconsistency	no serious indirectness	very serious(d)	none	4/56 (7.1%)	8/54 (14.8%)	RR 0.48 (0.15 to 1.51)	77 fewer per 1000 (from 126 fewer to 76 more)	VERY LOW	IMPORTANT
AKI- RIFLE-Injury – Sepsis (subgroup)[70]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1130/3265 (34.6%)	1253/3300 (38%)	RR 0.91 (0.85 to 0.97)	34 fewer per 1000 (from 11 fewer to 57 fewer)	HIGH	IMPORTANT
AKI- RIFLE-Failure [70]												
1	randomised trials	no serious risk of bias	no serious inconsistency	Serious(a)	Serious(e)	none	336/3243 (10.4%)	301/3263 (9.2%)	RR 1.12 (0.97 to 1.3)	11 more per 1000 (from 3 fewer to 28 more)	LOW	IMPORTANT
Use of renal replacement therapy [43,70]												
2	randomised trials	no serious risk of bias	no serious inconsistency	Serious(a)	Serious(e)	none	237/3408 (7%)	199/3429 (5.8%)	RR 1.2 (1 to 1.44)	12 more per 1000 (from 0 more to 26 more)	LOW	IMPORTANT
Use of renal replacement therapy – Trauma (subgroup) [43]												
1	randomised trials	Serious(b)	no serious inconsistency	no serious indirectness	very serious(d)	none	2/56 (3.6%)	3/54 (5.6%)	RR 0.64 (0.11 to 3.7)	20 fewer per 1000 (from 49 fewer to 150 more)	VERY LOW	IMPORTANT
Use of renal replacement therapy – Sepsis (subgroup) [70]												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Tetrastarch	Sodium Chloride 0.9%	Relative (95% CI)	Absolute		
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious(e)	none	235/3352 (7%)	196/3375 (5.8%)	RR 1.21 (1 to 1.45)	12 more per 1000 (from 0 more to 26 more)	HIGH	IMPORTANT

(a) Study (Myburgh 2012) conducted in patients in ICU and may not be generalisable to other patients receiving fluid resuscitation outside of ICU. Other studies were conducted in patients with sepsis Guidet2012) or trauma (James 2011) and may not be generalisable to all patients receiving fluid resuscitation.
(b) Difference in baseline characteristics of two groups- injury severity was greater in patients with blunt trauma who received 6% HES as compared to sodium chloride 0.9%; unclear if allocation concealment carried out or if investigators blinded.
(c) I2 value=74%, unexplained heterogeneity as both studies included sepsis patients, random effects analysis undertaken.
(d) Confidence interval crosses both MIDs
(e) Confidence interval crosses one MID.

Table 26: Clinical evidence profile: Tetrastarch compared to Ringer's acetate solution for fluid resuscitation

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Tetrsratch	Ringer's acetate	Relative (95% CI)	Absolute		
All cause mortality (30 days)[84]												
1	randomised trials	no serious risk of bias	no serious inconsistency	Serious(a)	no serious imprecision	none	154/398 (38.7%)	144/400 (36%)	RR 1.07 (0.9 to 1.29)	25 more per 1000 (from 36 fewer to 104 more)	MODERATE	CRITICAL
All cause mortality (90 days)[84]												
1	randomised trials	no serious risk of bias	no serious inconsistency	Serious(a)	no serious imprecision	none	201/398 (50.5%)	172/400 (43%)	RR 1.17 (1.01 to 1.36)	73 more per 1000 (from 4 more to 155 more)	MODERATE	CRITICAL
AKI- doubling of serum creatinine level[84]												
1	randomised trials	no serious risk of bias	no serious inconsistency	Serious(a)	Serious(b)	none	148/398 (37.2%)	127/400 (31.8%)	RR 1.17 (0.97 to 1.42)	54 more per 1000 (from 10 fewer to 133 more)	LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Tetrsratch**	**Ringer's acetate**	**Relative (95% CI)**	**Absolute**		
Use of mechanical ventilation[84]												
1	randomised trials	no serious risk of bias	no serious inconsistency	Serious(a)	no serious imprecision	none	325/398 (81.7%)	321/400 (80.3%)	RR 1.02 (0.95 to 1.09)	16 more per 1000 (from 40 fewer to 72 more)	MODERATE	IMPORTANT

(a)Study (Perner 2012) was conducted in patients with severe sepsis and findings may not be generalisable to all patients receiving intravenous fluids for fluid resuscitation.
(b) Crosses one MID.

7.2.2.2 Economic evidence

No economic studies were identified on the cost-effectiveness of hydroxyethylstarch vs sodium chloride 0.9% for intravenous fluid resuscitation of hospitalised patients.

An original cost analysis was developed to compare gelatin, hydroxyethylstarch (tetrastarch), albumin and crystalloids - see section 7.2.3.2.

7.2.2.3 Evidence statements

Clinical

Two studies with 6827 patients in critical care settings suggested that there may be no difference in all cause mortality at 30 days or at 90 days with the use of tetrastarch over sodium chloride 0.9%. The evidence was of moderate quality. However, two studies with 6837 patients showed that patients receiving tetrastarch were more likely to receive renal replacement therapy as compared to patients who had received sodium chloride 0.9% for fluid resuscitation. However, the same two studies also showed that fewer patients in the tetrastarch group met the RIFLE criteria for Risk and Injury. The evidence ranged from very low to moderate quality.

One study with 798 sepsis patients showed that there may be an increase in mortality at 90 days with the use of tetrastarch over lactated Ringer's solution. The evidence also showed that patients receiving tetrastarch may have an increase in acute kidney injury as compared to patients receiving lactated Ringer's solution. The evidence was of moderate quality.Economic

See section 7.2.3.3

7.2.2.4 Recommendations and link to evidence

See recommendations and link to evidence in section 7.4

7.2.3 Albumin

7.2.3.1 Clinical evidence

A Cochrane review[92] and one RCT were included in the review.[37] Evidence from these are summarised in the clinical GRADE evidence profile below. See also the forest plots in section G.3.3, Appendix G, study evidence tables in E.3.3, Appendix E and exclusion list in section H.3, Appendix H.

Table 27: Clinical evidence profile: Albumin vs. Sodium chloride 0.9%: Included studies for mortality outcome only (From Cochrane review) [92]

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Albumin	Sodium chloride 0.9%	Relative (95% CI)	Absolute	Quality	Importance
Mortality – All studies available[1,124]												
2	randomised trials	no serious risk of bias (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	727/3510 (20.7%)	729/3492 (20.9%)	OR 0.99 (0.88 to 1.11)	2 fewer per 1000 (from 20 fewer to 18 more)	HIGH	CRITICAL

(a) There were important differences in baseline risk across studies. Most of the information was from a large RCT in intensive care patients

Table 28: Clinical evidence profile: Albumin compared to sodium chloride 0.9%

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Albumin 4%	Sodium chloride 0.9% SAFE study	Relative (95% CI)	Absolute	Quality	Importance
All cause mortality - 28 days - All patients[1]												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious indirectness (a)	no serious imprecision	none	726/3473 (20.9%)	729/3460 (21.1%)	RR 0.99 (0.91 to 1.09)	2 fewer per 1000 (from 19 fewer to 19 more)	MODERATE	CRITICAL
All cause mortality - 28 days – Trauma subgroup[1]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	81/596 (13.6%)	59/590 (10%)	RR 1.36 (0.99 to 1.86)	36 more per 1000 (from 1 fewer to 86 more)	HIGH	CRITICAL
All cause mortality - 28 days - Severe Sepsis subgroup[1]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	185/603 (30.7%)	217/615 (35.3%)	RR 0.87 (0.74 to 1.02)	46 fewer per 1000 (from 92 fewer to 7 more)	HIGH	CRITICAL
All cause mortality - 28 days – ARDS (Acute Respiratory Distress Syndrome) subgroup[1]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	24/61 (39.3%)	28/66 (42.4%)	RR 0.93 (0.61 to 1.41)	30 fewer per 1000 (from 165 fewer to 174 more)	HIGH	CRITICAL
Morbidity (assessed with: New organ failure - SOFA score 3 or 4) [1]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1252/2649 (47.3%)	1249/2673 (46.7%)	RR 1.01 (0.96 to 1.07)	5 more per 1000 (from 19 fewer to 33 more)	HIGH	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Albumin 4%	Sodium chloride 0.9% SAFE study	Relative (95% CI)	Absolute		
Respiratory failure (measured with: Days with mechanical ventilation; Better indicated by lower values) [1]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	3473	3460	-	MD 0.19 higher (0.08 lower to 0.47 higher)	HIGH	CRITICAL
AKI (measured with: Duration of renal replacement therapy; Better indicated by lower values) [1]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	3473	3460	-	MD 0.09 higher (0 to 0.19 higher)	HIGH	CRITICAL
Volume of fluids used in ml - Study fluid - Day 1 (Better indicated by lower values) [1]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	3410	3460	-	MD 381.4 lower (442.13 to 320.67 lower)	HIGH	IMPORTANT
Volume of fluids used in ml - Non study fluid- Day 1 (Better indicated by lower values) [1]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	3392	3405	-	MD 46.2 lower (104.17 lower to 11.77 higher)	HIGH	CRITICAL
Length of Stay in days- Hospitalisation (Better indicated by lower values) [1]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	3473	3460	-	mean 0 higher (0.70 lower to 0.21 higher)	HIGH	CRITICAL
Length of Stay in days - ICU (Better indicated by lower values) [1]												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Albumin 4%**	**Sodium chloride 0.9% SAFE study**	**Relative (95% CI)**	**Absolute**		
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	3473	3460	-	MD 0.24 higher (0.06 to 0.54 higher)	HIGH	CRITICAL

(a) Study was conducted in patients with sepsis, trauma and these findings from these groups may not be applicable to all hospitalised patients.

7.2.3.2 Economic evidence

Published literature

One cost-effectiveness analysis was identified assessing the costs and effectiveness of two types of fluid used for fluid support. In one strategy, patients were given sodium chloride 0.9% while in the second, they were prescribed intravenous albumin 4%. [37] This is summarised in the economic evidence profile below (Table 29). See also the study selection flow chart in section J.3, in Appendix J and economic evidence table in section F.3, Appendix F

Five studies that were not relevant to the clinical question were not included. These are listed in section I.1, Appendix I with reasons for exclusion given.

Table 29: Economic evidence profile: Albumin 4% vs. Sodium chloride 0.9%

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Guidet [37]	Partially Applicable [(a)]	Potentially Serious Limitations [(b)]	Analysis developed from a French National Health Services perspective of patients with severe sepsis for fluid support	£191[(c)]	0.45 life years gained	£425 per life year gained	If the mortality difference is only 1% then the ICER=400% of the base case scenario (4.6%). If there is no mortality difference then saline infusion dominates. If quantity of albumin 4.5L, ICER= 200% base case scenario (2.25L).

(a) Some uncertainty about the applicability of French IV fluid costs to UK NHS setting.
(b) Cost difference between interventions based on additional cost of albumin and other unidentified costs. In-hospital costs assumed to be similar for both interventions
(c) 2005 Euros presented here as 2005 UK pounds

New cost analysis

The GDG considered the choice of resuscitation fluid to be a high priority for de novo economic modelling. However, the clinical review found little evidence of the relative clinical effectiveness of different fluid types, so a simple cost analysis was conducted with a threshold sensitivity analysis around the number of complications averted, see Appendix M.

It was assumed that administration costs would be similar for each fluid and therefore only fluid costs and complication costs were included. Fluid costs were provided by the NHS Commercial Medicines UnitThe cost of a major fluid-related complication (see 4.2.3) was estimated using NHS reference costs to be £1,868 (or £3,000 including a critical care episode).

The cost of each fluid is shown in Table 30 along with the number of complications that would need to be averted to make each fluid cost neutral. The lowest cost fluid was 0.9% Sodium chloride at £1.40 per patient – see Table.

The most expensive fluid, Albumin 4.5% cost £136.24 and would need to avert 45-72 major complications per 1000 patients to be cost neutral.

The analysis did not take account of fluid volume. In the clinical evidence there was little evidence of a difference in fluid volume, except in the case of albumin vs NaCl. But even here it is doubtful that this difference is large enough that a fewer number of bags could be used. Furthermore, if one less bag was required then albumin would still be the most costly fluid in terms of acquisition cost and that's not even considering the additional costs associated with storing and administering albumin.

This analysis can be considered as partially applicable (since NHS unit costs were used but QALYs were not estimated. Furthermore, conclusions about cost-effectiveness or cost neutrality are not possible without evidence of the number of complications averted.

Table 30: Cost of fluids for resuscitation

Resuscitation fluid regimen (in order of cost of fluid per patient)	Cost of fluid for resuscitation (2000ml) [(a)]	Number of extra major complications per 1000 patients that must be avoided for fluid to be cost neutral compared with 0.9% Sodium chloride (including critical care costs)
0.9% Sodium chloride	£1.40	-
Hartmann's solution	£1.70	<1
Plasma-Lyte M	£1.84	<1
Ringer's Lactate	£5.00	2 (1)
Volplex	£7.60	3 (2)
Isoplex	£7.80	3 (2)
Gelofusine/Gelaspan 4%	£9.60	4 (3)
Geloplasma	£10.00	5 (3)
6% Venofundin	£25.20	13 (8)
6% Tetraspan	£26.00	13 (8)
6% Voluven	£30.00	15 (10)
6% Volulyte	£30.60	16 (10)
10% Tetraspan	£39.60	20 (13)
5% Albumin	£122.08	65 (40)
4.5% Albumin	£136.24	72 (45)

(a)Total cost for fluid resuscitation based on unit costs of 250ml or 500ml bags only when unit costs for 1000 ml bags were not available. It is noted that on a local contract, the availability of bag size may differ.

7.2.3.3 Evidence statements

Clinical

Overall, there were no clinically important differences in any of the outcomes (all cause mortality, morbidity, AKI, respiratory failure, length of stay in ICU and overall length of stay in hospital) identified for the comparison of albumin 4% vs sodium chloride 0.9%.

However, when mortality data of the SAFE study were analysed according to the study's pre-specified subgroup, there may be a clinically important reduction in mortality in the sepsis subgroup in the albumin treatment arm compared with the sodium chloride 0.9% treatment arm. In the trauma subgroup, there may be an increase in mortality in the albumin treatment arm compared to the sodium chloride 0.9% treatment arm. Neither of these differences in these subgroups reached statistically significance even without correction for multiple testing. Further analysis of the trauma subgroup showed that virtually all the excess mortality in the albumin group was among patients with severe traumatic brain injury.[69]The quality of evidence was high for all of the outcomes except for mortality whre the evidence was of moderate quality.

Economic

One cost–effectiveness analysis found that albumin 4% was cost effective compared to sodium chloride 0.9% for fluid resuscitation in patients with severe sepsis (ICER: £425 per life-year gained). This analysis was assessed as partially applicable with potentially serious limitations.

An original comparative cost analysis showed that:

- Sodium Chloride 0.9% was the cheapest fluid for resuscitation.
- Balanced physiological solutions would need to avert up to 2 complications per 1000 patients to be cost neutral.
- Gelatin would need to avert 2-5 complications per 1000 patients to be cost neutral.
- Tetrastarches would need to avert 8-20 complications per 1000 patients to be cost neutral.
- Albumin would need to avert 40-72 complications per 1000 patients to be cost neutral.

This analysis was assessed as partially applicable with potentially serious limitations.

7.2.3.4 Recommendations and link to evidence

See recommendations and link to evidence in section 7.4

7.2.4 Buffered/physiological solutions

Comparisons: Buffered/physiological solutions vs. sodium chloride 0.9% solution.

7.2.4.1 Clinical evidence

No RCT was identified for the following comparisons:

- balanced physiological solutions vs. sodium chloride 0.9%
- colloids in balanced physiological solutions vs. colloids in sodium chloride 0.9%

One Cochrane review was identified which appeared to be relevant to this review question. [14] However, this was excluded as:

- the analysis of outcomes of interest was from studies with populations or interventions that were out of scope of this guidance or were too indirect to the review population
  - intra-operative cardiac surgery patients [8]
  - Use of hetastarches[31]
  - Renal transplant patients [79]
- Outcomes were assessed at different time frames to that of the review protocol (mortality was assessed for all time frames)

The list of excluded studies and reasons for exclusions are shown in section H.3, Appendix H.

7.2.4.2 Economic evidence

No economic studies were identified on the cost-effectiveness of buffered/physiological solutions vs. sodium chloride 0.9% for intravenous fluid resuscitation of hospitalised patients. An original cost analysis was developed to compare gelatin, hydroxyethylstarch (tetrastarch), albumin and crystalloids (see section 7.2.3.2)

7.2.4.3 Evidence statements

Clinical

No studies comparing balanced physiological solution such as Ringer's lactated solution vs Sodium chloride 0.9% for patients requiring IV fluid resuscitation were found.

Economic

See section 7.2.3.3.

7.3 Volumes and timing

The objective of this review was to find out whether factors such as when fluid should be initiated, rate of administration (ml/kg/hour), total volume (ml/kg/day) and administering fluids continuously over 24 hours vs. intermittently, affect the safety and efficacy of fluid resuscitation management.

Review questions:

What are the most clinically and cost effective timings and rate of administration of intravenous fluids in fluid resuscitation?

What is clinical and cost effectiveness of different volumes of fluid administration in patients requiring fluid resuscitation?

We searched for RCTs comparing the effectiveness of varying volumes, timing and/or rate of fluid administration between treatment arms. Only those fluids found to be clinically and cost- effective in the reviews reported in section 7.2 of types of fluid for resuscitation were included in this review.

For more details see review protocol in section C.3 in Appendix C.

7.3.1 Clinical evidence: Volumes and timing

We found 6 RCTs investigating the effects of volume and timing[27,53,65,91,120] :

- Timing of fluid resuscitation (early vs. delayed/control group): 3 studies; 1 study in penetrating trauma patients(Bickell1994[11]), 2 in sepsis patients (Rivers2001[91], Lin2006[53])
- Rate of fluid administration: 1 study in acute pancreatitis patients(Mao 2009[65])
- Low volume (conservative therapy) vs. high volume (liberal): 2 studies; 1 in acute lung injury patients (Wiedemann[120]), 1 in trauma patients (Dutton2002[27])

All these studies were undertaken in very specific patient groups; the results may not therefore be applicable to the general patients in hospital. See evidence table in section E.3.4 in Appendix E for more details on populations and interventions.

See also study exclusion list in section H.3, in Appendix H

Table 31: Clinical evidence profile: Early vs delayed fluid resuscitation

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Early	Control	Relative (95% CI)	Absolute	Quality	Importance
All cause mortality [11]												
Subgroup of trauma patients (haemorrhage)												
1	randomised trials	serious(a)	no serious inconsistency	very serious(b)	no serious imprecision	none	116/309 (37.5%)	86/289 (29.8%)	RR 1.26 (1 to 1.58)	77 more per 1000 (from 0 more to 173 more)	VERY LOW	CRITICAL
Subgroup of sepsis patients[53,91]												
2	randomised trials	serious(a)	no serious inconsistency	serious(b)	no serious imprecision	none	98/238 (41.2%)	144/249 (58.7%)	RR 0.72 (0.60 to 0.86)	164 fewer per 1000 (from 82 fewer to 235 fewer)	LOW	CRITICAL
Renal Failure(e)												
Subgroup of trauma patients (haemorrhage) [11]												
1	randomised trials	serious(a)	no serious inconsistency	very serious(b)	serious(c)	none	8/227 (3.5%)	3/360 (1.2%)	RR3.5(0.82, 11.38)	25 more per 1000 (from 2 fewer to 125 more)	VERY LOW	IMPORTANT
Subgroup of sepsis patients[53]												
1	randomised trials	serious(a)	no serious inconsistency	serious(b)	serious(c)	none	42/108 (38.9%)	64/116 (55.2%)	RR 0.7 (0.53 to 0.94)	166 fewer per 1000 (from 33 fewer to 259 fewer)	VERY LOW	IMPORTANT
Respiratory failure- Duration of mechanical ventilation (days) (Better indicated by lower values) [11,53]												
2	randomised trials	serious(a)	no serious inconsistency	serious(b)	serious(c)	none	180	210	-	MD 2.95 lower (8.73 lower to 2.83 higher)	VERY LOW	IMPORTANT
Length of hospitalisation (days) (Better indicated by lower values)(f) [11,53,91]												
3	randomised trials	serious(a),(d)	no serious inconsistency	serious(b)	serious(c)	none	465	487	-	MD 1.58 higher (0.76 lower to 3.92 higher)	VERY LOW	IMPORTANT
Length of hospitalisation among patients who survived until discharge (days) (Better indicated by lower values)(f) [11]												
Subgroup of trauma patients (haemorrhage)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Early**	**Control**	**Relative (95% CI)**	**Absolute**		
1	randomised trials	serious(a),(d)	no serious inconsistency	serious(b)	serious(c)	none	227	238	-	MD 3 higher (0.95 lower to 6.95 higher)	VERY LOW	IMPORTANT
Subgroup of sepsis patients [91]												
1	randomised trials	serious(a),(d)	no serious inconsistency	serious(b)	serious(c)	none	92	74	-	MD 3.8 lower (8.32 lower to 0.72 higher	VERY LOW	IMPORTANT
Length of ICU stay (days) (Better indicated by lower values) [11,53]												
2	randomised trials	serious(a),(d)	no serious inconsistency	serious(b)	serious(c)	none	335	354	-	MD 1.17 lower (3.25 lower to 0.91 higher)	VERY LOW	IMPORTANT
Morbidity – not reported												
Quality of life – not reported												

(a) Serious limitations due to lack of description randomisation, allocation concealment and blinding methods. Bickell1994 is a quasi randomised study [11]Studies in of early goal directed therapy[53,91] have a protocol for the intervention group, but lack a protocol for the control group. This presence of a protocol vs lack of protocol could affect other areas of intervention.

(b) Studies were conducted in specific groups of patients (haemorrhagic shock in penetrating trauma patients[11], sepsis [53,91], acute lung injury[120]), with uncertain applicability to the majority of patients in the guideline.

(c) Confidence intervals wide, crossing the MIDs.

(d) One study, Lin2006 [53] reported average LOS for all patients enrolled. Bickell1994 [11] reported average of patients who survived, The sample size used for calculation in one study was unclear (Rivers2001[91]), most likely had used average of all patients enrolled for LOS (hospitalisation), but LOS of only patients who survived until discharge in LOS (hospitalisation) of survivors (data analysed in the sensitivity analysis).

(e) Bickell1994 [11] only reported data for patients who survived the operation.Lin2006[53] reported data for the whole cohort.

(f) Sensitivity analysis of length of stay data for whole cohort and survivors only conducted

Table 32: Clinical evidence profile: Fast vs. controlled rate of fluid resuscitation

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Fast**	**Controlled**	**Relative (95% CI)**	**Absolute**		
All cause mortality[65]												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Fast**	**Controlled**	**Relative (95% CI)**	**Absolute**		
1	randomised trials	serious(a)	no serious inconsistency	serious(b)	no serious imprecision	none	11/36 (30.6%)	4/40 (10%)	RR 3.06 (1.07 to 8.75)	206 more per 1000 (from 7 more to 775 more)	LOW	CRITICAL
Morbidity (APACHE score) (Better indicated by lower values) [65]												
1	randomised trials	serious(a)	no serious inconsistency	serious(b)	serious(c)	none	36	40	-	MD 3.3 higher (0.66 to 5.94 higher)	VERY LOW	CRITICAL
Quality of life – not reported												
Respiratory failure - not reported												
Renal failure – not reported												
Length of hospital/ICU stay – not reported												

(a)Serious limitations due to lack of description randomisation, allocation concealment and blinding methods.
(b)Study was conducted in patients with acute pancreatitis, unclear its applicability to the general guideline population.
(c)Wide confidence intervals crossing MID. Small sample size

Table 33: Clinical evidence profile: High vs low volume fluid resuscitation

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Low**	**High volume**	**Relative (95% CI)**	**Absolute**		
All cause mortality [27,120]												
2	randomised trials	no serious risk of bias	no serious inconsistency	serious	no serious imprecision	none	132/558 (23.7%)	26.3%	RR 0.9 (0.73 to 1.1)	26 fewer per 1000 (from 71 fewer to 26 more)	MODERATE	CRITICAL
Renal Failure, receiving renal replacement therapy[120]												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious(a)	serious(b)	none	50/503 (9.9%)	14.1%	RR 0.71 (0.5 to 0.99)	42 fewer per 1000 (from 1 fewer to 71 fewer)	LOW	CRITICAL
Respiratory failure, measured by ventilator free days (within first 28 days) (Better indicated by higher values) [120]												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious(a)	serious(b)	none	503	497	-	MD 2.5 higher (1.11 to 3.89 higher)	LOW	CRITICAL
ICU free days (within first 28 days) (Better indicated by higher values) [120]												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious(a)	serious(b)	none	503	497	-	MD 2.2 higher (1.09 to 3.31 higher)	LOW	IMPORTANT
Quality of life – not reported												
Length of hospital stay – not reported												

(a) Both studies were conducted in specific groups of patients; Dutton 2002 was conducted in trauma patients, Wiedemann2006 were conducted in intubated acute lung injury patients. Applicability to guideline population unclear
(b) Confidence intervals crossed MIDs

7.3.2 Economic evidence

No economic studies were identified on the cost-effectiveness of different volumes of fluid administration for intravenous fluid resuscitation of hospitalised patients.

No economic studies were identified on the cost-effectiveness of different timings for the administration of intravenous fluid resuscitation of hospitalised patients.

7.3.3 Evidence statements

Clinical

Early vs. late administration of IV fluid for resuscitation

There was a potential clinically important increase in all-cause mortality, length of hospitalisation for survivors, and renal failure in the group receiving early treatment compared to delayed treatment for patients with trauma, but a clinically important decrease in these parameters in patients receiving early IV fluid resuscitation for sepsis, although evidence in all the studies was very low quality.

There was a decrease in respiratory failure for patients receiving early administration of IV fluid, but although two studies suggested that there may be about a 1 day saving in length of ICU stay, there was considerable uncertainty and the evidence was of very low quality.

No studies reported morbidity and quality of life outcomes.

Fast vs. controlled rate of fluid resuscitation

There was clinically important increase in all cause mortality and morbidity among acute pancreatitis patients receiving faster rate of fluid administration as compared to those receiving controlled rates of IV fluid administration. The evidence was low quality for all cause mortality and of very low quality for morbidity.

No studies reported quality of life, acute kidney injury, respiratory failure, length of hospitalisation or ICU stay.

High vs low volume fluid resuscitation

There were no clinically important differences in all cause mortality for patients receiving higher or lower fluid volume. The evidence ranged from moderate (only for all cause mortality) to low quality.

There may be clinically important decrease in renal failure, respiratory failure and length of ICU stay among patients receiving lower fluid volume.

No studies reported quality of life and length of hospitalisation.

Economic

No economic evidence was found on this question

7.4 Recommendations and link to evidence

Recommendations	**16. If patients need IV fluid resuscitation, use crystalloids that contain sodium in the range 130–154 mmol/l, with a bolus of 500 ml over less than 15 minutes. (For more information see the Composition of commonly used crystalloids table.)** **17. Do not use tetrastarch for fluid resuscitation.** **18. Consider human albumin solution 4–5% for fluid resuscitation only in patients with severe sepsis.**
Relative values of different outcomes	The GDG were interested in all cause mortality, length of hospital stay, complications including renal and respiratory problems, and morbidity as measured by SOFA or MODS scores. All cause mortality was considered to be the critical outcome for decision-making, although all other outcomes were deemed as important for informing recommendations. Mortality at 30 days was considered to be the most critical outcome relevant to patients receiving IV fluids for resuscitation in admission or general ward settings but the GDG also considered mortality at 90 days for decision making. Morbidity and development of complications, acute kidney injury and length of stay in ICU and hospital were considered as important outcomes. They were also interested in the volumes of fluid infused for studies comparing different fluid types for resuscitation, as success with fluid resuscitation achieved with a lower volume, implies that the fluid used might have better intravascular expanding properties.
Trade off between clinical benefits and harms	Summary of the evidence: The reviews on the use of different fluid types for resuscitation indicated the following: • no consistent advantage or disadvantage for the use of gelatin compared with tetrastarch in terms of mortality, the volume of fluid needed to be infused for fluid resuscitation • no clear evidence that the use of gelatin granted significant advantage or disadvantage over the use of either Ringer's lactate or 0.9% sodium chloride in terms of mortality. • no evidence of clinical benefit with the use of starches over crystalloids for fluid resuscitation. The clinical evidence review found no difference in all cause mortality with the use of tetrastarches over sodium chloride 0.9% at 30 days (RR 1.07 [0.96 to 1.21]) and at 90 days (RR 1.07 [0.97 to 1.18]. On comparison of tetrastarches with lactated Ringer's solution, again there was no difference in mortality at 30 days (RR 1.07 [0.9 to 1.29]). There was an increase in 90-day mortality with tetrastarch compared with Ringer's acetate in patients with sepsis (RR 1.17 [1.01 to 1.36]). There was an increase of 8% in the absolute risk of mortality with the use of tetrastarches over Ringer's acetate. Overall, there were no clinically important differences in outcomes in the

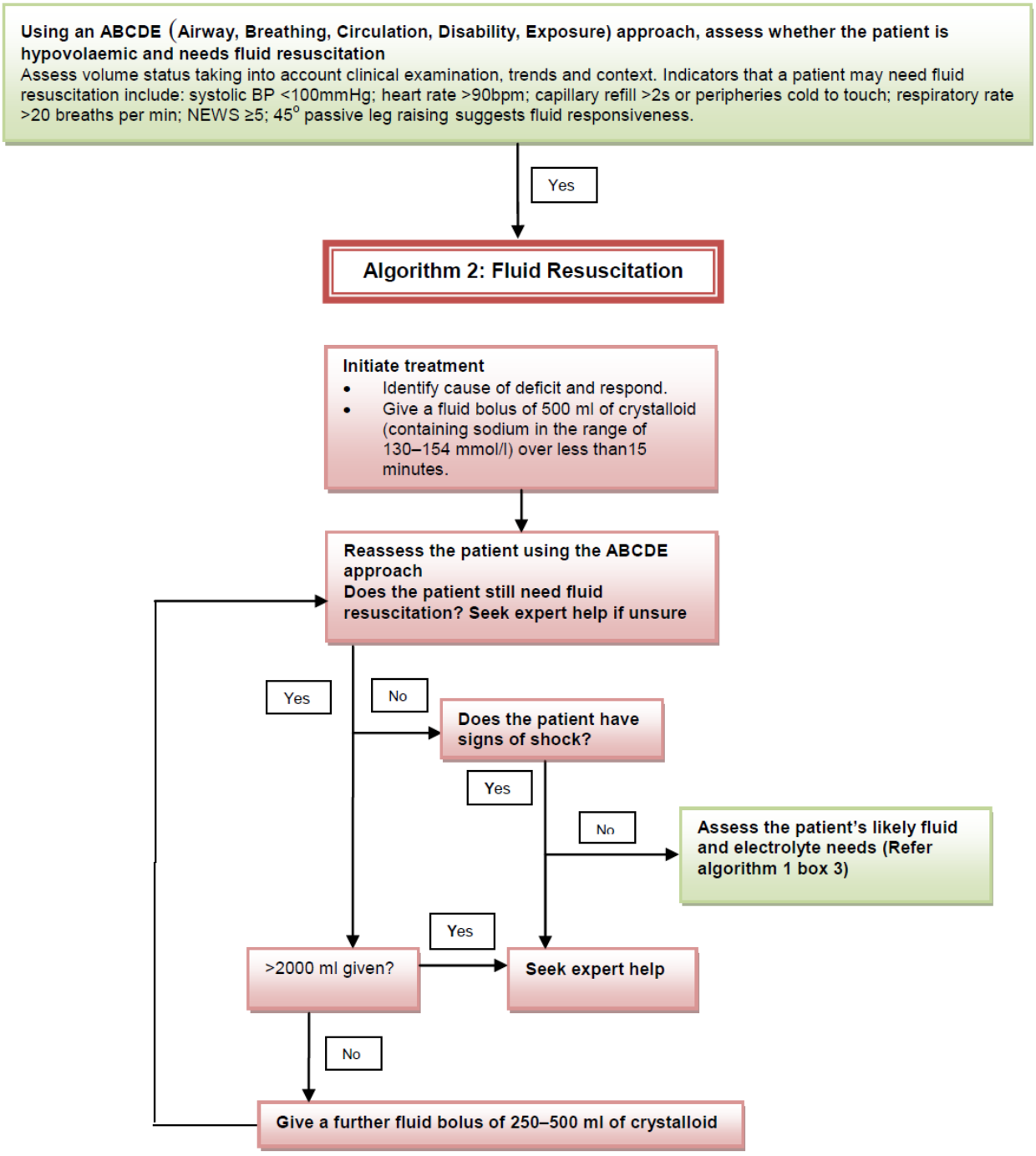
	studies that compared albumin 4% with sodium chloride 0.9% for fluid resuscitation in terms of all cause mortality, morbidity, AKI, respiratory failure, length of stay in ICU and overall length of stay in hospital. There was evidence of clinical benefit with the use of albumin in patients with severe sepsis. Mortality data from the SAFE study suggested that there may be a clinically important reduction in mortality in sepsis when albumin is used compared to 0.9% sodium chloride, whilst in the trauma subgroup, there may be an increase in mortality when albumin is used compared to 0.9% sodium chloride. No clinical evidence was identified for the following comparisons: • gelatin or hydroxyethylstarch vs. Hartmann's • balanced physiological solutions vs. sodium chloride 0.9% • colloids in balanced physiological solutions vs. colloids in sodium chloride 0.9% Therefore the GDG prioritised research recommendations evaluating these comparisons(see section 7.5) The reviews on the volumes and timings of fluids for fluid resuscitation indicated the following: *Early vs. late administration of IV fluid for fluid resuscitation* There was a potentially clinically important increase in all-cause mortality, length of hospitalisation for survivors, and renal failure in a group receiving early IV fluid resuscitation compared to delayed treatment for patients with trauma. Conversely, however, there was a clinically important decrease in these parameters in patients receiving early IV fluid resuscitation for sepsis, although evidence in all the studies was very low quality. There was a potentially a clinically important decrease in respiratory failure for patients receiving early administration of IV fluid but, although two studies suggested that there may also be about a 1 day saving in length of ICU stay with early administration, there was considerable uncertainty and the evidence was of very low quality. No studies of early vs. late administration of IV fluids for resuscitation reported morbidity and quality of life outcomes. *Fast vs. controlled rate of fluid resuscitation* There were clinically important increase in all cause mortality and morbidity among acute pancreatitis patients receiving fast vs. controlled rates of IV fluid administration. No studies reported quality of life, acute kidney injury, respiratory failure, length of hospitalisation or ICU stay. *High vs. low volume fluid resuscitation* Overall, there were no clinically important differences in all cause mortality for patients receiving higher or lower fluid volumes but there may be clinically important decreases in renal failure, respiratory failure and length of ICU stay for patients who receive lower fluid volumes. No studies reported quality of life and length of hospitalisation.
Economic considerations	A simple cost analysis was conducted. In the absence of evidence of differences in complications, crystalloids were the lowest cost fluids followed by gelatin and then tetrastarches; albumin was the highest cost. Crystalloids: Since they are the cheapest and at no apparent clinical disadvantage, crystalloids appear to be the most cost-effective fluid for most

	patients. Hence in most circumstances a move from colloids to crystalloids would be expected to lead to cost saving as well as leading to improvement (or at least no detriment) to health outcome. Since tetrastarches are more costly and were associated with an increase in mortality,it is unlikely that they could be cost-effective. Unless evidence of clear benefit is forthcoming in other patient groups, the GDG recommend that tetrastarch is not used outside of clinical trials. Gelatin is more costly than crystalloids and there was no evidence of a clinical benefit with its use over crystalloids and therefore its cost-effectiveness is unproven – see research recommendation. Albumin: For patients with severe sepsis, the use of albumin infusion for fluid support was found by a French economic evaluation to be cost-effective compared with 0.9% sodium chloride based on the sepsis subgroup from the SAFE study. Albumin 4% costs more but this was outweighed by the survival benefit.
Quality of evidence	The quality of evidence on the use of different types of fluids for resuscitation ranged from very low to high quality. Evidence on the use of gelatin for fluid resuscitation was mainly of very low quality for majority of the outcomes. There was evidence of lack of effectiveness and some evidence of harm (increase in mortality) with the use of tetrastarches for fluid resuscitation in patients with sepsis. The evidence for the critical outcome (mortality) when comparing tetrastarches to crystalloids was of moderate quality (downgraded due to indirectness). Quality of evidence for other important outcomes including morbidity, length of stay in hospital and ICU ranged from moderate to low quality. The evidence of effectiveness for the use of albumin in patients with sepsis was of moderate to high quality. Other than that pertaining to the use of albumin and tetrastarches for fluid resuscitation, much of the evidence in the reviews presented in this chapter on the best type of fluid to use and the optimal volume, timing and rate of its administration was of low or very low quality, with major limitations in the design of studies which increase the risk of bias. A major issue with this review (and other reviews in this guideline) has been the breadth of the target population, which includes all hospitalised patients. As a result, evidence found in relation to specific groups of patients (as was mostly the case) was judged to be indirect to the whole target population and the evidence was downgraded for this. The evidence from the trials identified may have limited applicability to the situation where basic guidance for IV fluid resuscitation in hospital admission units and general ward areas is needed for clinicians with relatively limited experience. Most trials were carried out in either: • operating suites - where much of the need for 'fluid resuscitation' for subjects likely to be eligible for a trial relates to the need to maintain intravascular volume in the face of anaesthetic induced vasodilatation; or • Intensive care settings - where many cases needing IV fluid 'resuscitation' are effectively in 'second line' situations rather than the 'first line' therapy situation when fluid resuscitation is needed in admission or general ward areas The inclusion of different groups and different interaction of the interventions in these specific groups created considerable heterogeneity - this was considered when assessing the quality of evidence.

	. The evidence from trials on fluid resuscitation was difficult to analyse (combine for a meta-analysis) because the types and volumes of fluid, timing of initiation and rates of administration varied considerably. Some trials also included the use of different inotropes. Quality of evidence for studies on volume and timing of fluids for resuscitation was low to very low for all critical outcomes. There are major limitations in the design of studies, which increase the risk of bias. The studies on early vs. late administration of IV fluid resuscitation were conducted in specific populations (e.g. penetrating trauma, septic shock, acute lung injury patients) that may well not be representative of the more general hospital populations who are the focus of this guideline. Patients with penetrating trauma in particular, may respond differently (as suggested by subgroup evidence) since early fluid resuscitation (before surgery) may increase blood pressure and dilute coagulation factors, increasing the risk of further bleeding. There is also a concern that the study populations were relatively young and that elderly patients may not be able to tolerate fast and high volume fluid resuscitation as well as younger patients. For these reasons, the evidence was downgraded for indirectness. The cost-effectiveness analysis of albumin was assessed as partially applicable, since it was conducted from a French health care perspective and therefore the resource use and cost may not be entirely transferable to a UK NHS setting. It was also assessed as having potentially serious limitations as the non-drug costs were not adequately described.
Other considerations	The GDG considered the findings from the evidence reviews on types, volumes and timings of fluid administration when drafting the recommendations for this review. An updated Cochrane review comparing crystalloids to colloids for fluid resuscitation in critically ill patients published in February 2013[83] was also discussed by the GDG. Although different in many aspects with respect to the review protocol and therefore not included in this guideline (the Cochrane review included studies on patients with burns and traumatic brain injury that were out of the scope of this guideline, included pentastarches, hexastarches and hyper-oncotic crystalloids and colloids as comparators and also included studies conducted before 1990), the review included certain populations and interventions which were relevant to this review. Findings from this Cochrane review echo the findings of this clinical evidence review with respect to effect sizes of mortality when comparing crystalloids to colloids. The GDG took this into consideration as significant additional evidence when making the recommendations. The GDG considered the absolute increase in mortality when making the recommendations. Default values of the minimal clinically important differences (0.75- 1.25) when assessing the relative risk were agreed to be inappropriate when deciding upon the clinical importance of mortality as an outcome and the decision of the GDG was based on effect size of the absolute risk difference in mortality. The recommendation for the use of crystalloids for fluid resuscitation was based on moderate quality clinical evidence and the evidence for cost-effectiveness of crystalloids. This recommendation was agreed to be a key priority for implementation. The recommendation for notusing tetrastarch for fluid resuscitation was based on the evidence of an increase in mortality in the long term (mortality at 90 days). Although this evidence was from patients with sepsis and was downgraded for indirectness, the GDG considered that it still was applicable to all patients receiving fluid resuscitation as a significant

	proportion may have underlying sepsis. The recommendation of the use of human albumin solution for fluid resuscitation of patients with sepsis is based on the evidence from the reviews presented including the economic analysis which supported its use. However, the GDG recognized that there were considerable practical/supply issues that would limit its widespread usage in non-specialist settings. Recommendation 16 was identified as a key priority for implementation. The GDG considered the extent to which this recommendation might change practice and what was needed to implement this. The GDG agreed that it was important that this recommendation was considered in accordance with the algorithm outlined for fluid resuscitation (refer recommendation 4 and algorithm 2). Note: During the period of stakeholder consultation on this guideline (on 27th June, 2013), a Class 2 Drug Alert was issued by the Medicines and Health Regulatory Authority (MHRA), UK recalling all unexpired stock of hydroxyethyl starches. The alert was based on findings of large RCTs which reported an increased risk of renal dysfunction and mortality in critically ill or septic patients who received hydroxyethyl starch compared with those who received crystalloids. The GDG also considered this decision of the MHRA and its implications while drafting the recommendation to not use tetrastarches for fluid resuscitation. The GDG discussed the findings and its relevance to early 'on ward' fluid resuscitation with colloid solutions and agreed that the evidence on this was still inconclusive and drafted a recommendation for further research which aims to compare the effectiveness of balanced crystalloids with a combination of a balanced crystalloid and a gelatin suspended in a balanced solution for fluid resuscitation of patients with acute hypovolaemic shock (see research recommendation 3, also see research recommendation protocol in Appendix O).

7.4.1 Algorithm 2: Fluid Resuscitation


Using an ABCDE (Airway, Breathing, Circulation, Disability, Exposure) approach, assess whether the patient is hypovolaemic and needs fluid resuscitation
Assess volume status taking into account clinical examination, trends and context. Indicators that a patient may need fluid resuscitation include: systolic BP <100mmHg; heart rate >90bpm; capillary refill >2s or peripheries cold to touch; respiratory rate >20 breaths per min; NEWS ≥5; 45° passive leg raising suggests fluid responsiveness.
Yes
Algorithm 2: Fluid Resuscitation
Initiate treatment
Identify cause of deficit and respond.
Give a fluid bolus of 500 ml of crystalloid (containing sodium in the range of 130–154 mmol/l) over less than15 minutes.
Reassess the patient using the ABCDE approach
Does the patient still need fluid resuscitation? Seek expert help if unsure
Yes
No
Does the patient have signs of shock?
Yes
No
Assess the patient's likely fluid and electrolyte needs (Refer algorithm 1 box 3)
Yes
>2000 ml given?
Seek expert help
No
Give a further fluid bolus of 250–500 ml of crystalloid

This section links the evidence to Algorithm 2 and the recommendation bullet specific to resuscitation.

Recommendations	**Offer IV fluid therapy as part of a protocol (see Algorithms for IV fluid therapy):** • **Assess patients' fluid and electrolyte needs following Algorithm 1: Assessment.** • **If patients need IV fluids for fluid resuscitation, follow Algorithm 2: Fluid resuscitation.** • **If patients need IV fluids for routine maintenance, follow Algorithm 3: Routine maintenance.** • **If patients need IV fluids to address existing deficits or excesses, ongoing abnormal losses or abnormal fluid distribution, follow Algorithm 4: Replacement and redistribution.**
Relative values of different outcomes	The GDG were interested in all cause mortality, length of hospital stay, complications including renal and respiratory problems, and morbidity as measured by Sequential Organ Failure Assessment (SOFA) scores. All cause mortality was considered to be the most important outcome for decision making, although all other outcomes were deemed as important for informing recommendations.
Trade off between clinical benefits and harms	The algorithm for fluid resuscitation was based on: • evidence based on the principles of fluid prescribing as described in section 5.1 • the reviews of the use of algorithms in fluid prescribing described in section 5.2 • guidance on the assessment of patients according to the NEWS score [95] • guidance on the non-fluid based elements recommended for resuscitation contained current Advanced Life Support guidance [5] • the evidence reviews informing the type, volume and timing of fluid administration for resuscitation (see section 7.3) This approach allowed the GDG to develop the complete resuscitation algorithm as well as some specific recommendations on IV fluid therapy for resuscitation. Assessment of the need for fluid resuscitation was based on National Early Warning Score (NEWS) criteria and NICE CG50.[16,95] From the six routinely monitored physiological parameters, the GDG identified pulse, blood pressure and respiratory rate as the key clinical markers of the sympathetic response to physiological decompensation. In addition the GDG agreed that prolonged capillary refill time and cool peripheries were important signs of reduced tissue perfusion secondary to the sympathetic response to shock that should be identified on initial assessment of need for fluid resuscitation.
Economic considerations	In section 5.2.3 it was noted that for patients with sepsis, protocolised care was found to be cost-effective for sepsis patients in two studies and cost saving in a third study. This evidence was considered to be partially applicable and with potentially serious limitations. There was no cost-effectiveness evidence for patients without sepsis.

	However, given that the health improvements observed in the review of clinical effectiveness evidence were just as pronounced for intra-operative care the GDG felt that the economic benefits of protocols are very likely to be achievable across all settings.
Quality of evidence	The algorithm was based on established guidance (NEWS, ALS guidance), consensus opinion of the GDG members and findings from the systematic reviews undertaken for determining the most clinical and cost-effective type, volume and timing of fluids to be used for resuscitation and the review on clinical effectiveness of protocolised care. Quality of evidence for outcomes analysed in the systematic reviews ranged from very low to high. For details on quality of evidence for individual reviews, refer sections 5.2, 7.2 and 7.3.
Other considerations	Despite the paucity of evidence on the use of protocols for IV fluid administration (see section 5.2), the GDG felt that protocolised care in general achieves better outcomes for patients and therefore decided that an algorithmic approach to fluid resuscitation is appropriate in this context. In designing the algorithm, the GDG placed particular emphasis on developing recommendations that a foundation year doctor could follow via the protocol to initiate appropriate resuscitation treatment as a first responder. The recommendations and protocol contained within the algorithm on the type, volume, timing and rate of IV fluid use for resuscitation are based on: •the principles of fluid prescribing described in section 5.1 •the reviews of evidence related to the use of algorithms in fluid prescribing described in section 5.2 •the evidence reviews on fluid type, volume, rate and timing presented here; and •the consensus expert views of the GDG. The non-fluid prescription elements incorporated in the algorithm including those on assessment for resuscitation and the non-fluid urgent treatments such as high-flow oxygen and securing intravenous access are in line with Advanced Life Support (ALS) guidance [90]. Administration of fluid boluses according to body weight was recommended by the GDG as a safe and effective approach to fluid resuscitation, although as with other approaches regular reassessment of the patient is needed. The use of 500 ml of fluid bolus for fluid resuscitation was based on GDG consensus. The GDG agreed that recognition of the seriously ill patient with a NEWS score of 5 or more should prompt seeking of expert help, alongside the initiation of resuscitation. The GDG consensus on 'senior input' was as defined by NICE CG50.[16]

7.5 Research recommendations

2. Are balanced solutions superior to sodium chloride 0.9% for the fluid resuscitation of patients with acute hypovolaemic shock?

Why this is important

Physiological studies, large cohort studies and small randomised studies have shown that balanced crystalloids may be superior to sodium chloride 0.9% for the treatment of surgical patients. However, the quality of the evidence is poor. These studies have shown that, when compared with sodium chloride 0.9%, there is less disturbance in acid–base balance (hyperchloraemic acidosis), acute kidney injury, the need for renal replacement therapy, blood loss and overall complication rates with balanced crystalloids. However, large randomised trials have shown that crystalloids are superior to colloids for resuscitation. In these studies colloids were given for prolonged periods of time and the groups of patients included were heterogenous. The proposed trial will help validate whether the data gathered from physiological studies and cohort studies that compared sodium chloride 0.9% with balanced crystalloids translate into relevant clinical benefit in patients needing acute fluid resuscitation, and will be a valuable guide to clinical practice.

3. **Are balanced crystalloids superior to a combination of a balanced crystalloid and a gelatin suspended in a balanced solution for the fluid resuscitation of patients with acute hypovolaemic shock?**

Why this is important

Recent large randomised controlled trials suggest that crystalloids (sodium chloride 0.9% or balanced solutions) are superior to 6% hydroxyethyl starch for resuscitation. Mortality and complication rates, especially renal complications, may be increased with 6% hydroxyethyl starch. However, there is a lack of good-quality evidence on the use of gelatin for resuscitation. Some randomised controlled trials have shown that when colloids are used for resuscitation, volumes of fluid required may be less than with crystalloids. It must be remembered that colloids cannot be used exclusively for resuscitation and that some free water must be provided, and there are limited data on the use of gelatins for resuscitation. The proposed trial will help inform whether a combination of gelatin and crystalloid is superior to crystalloid alone for the resuscitation of patients with acute shock.

4. **When undertaking perioperative goal-directed fluid therapy, does the choice of fluid affect complications and hospital length of stay?**

Why this is important

Several studies have shown reduced lengths of stay and reduced complications after a variety of surgical procedures when fluid therapy is optimised by targeting various haemodynamic goals (goal-directed therapy [GDT]). The most common haemodynamic goal has been optimal stroke volume, as measured by oesophageal doppler or an alternative non-invasive technique .Most studies have used colloids (hydroxyethyl starch or gelatine), although some have used crystalloid.

Colloids are more expensive than crystalloids and recent data indicate that hydroxyethyl starch is associated with an increased risk of acute kidney injury in patients with sepsis. If colloids are to be used as the default fluid for perioperative GDT, there should be clear evidence for their benefit over crystalloids.

There is evidence showing benefit of physiological (or balanced) fluids compared with saline-based fluids; therefore, it would seem appropriate to undertake a blinded, randomised controlled trial of colloid in balanced solution compared with a balanced crystalloid solution for perioperative GDT. If mortality is to be the primary end point for such a study, then prohibitively large numbers of patients would need to be enrolled. Other achievable outcomes include hospital length of stay, recovery of gut function (for gastrointestinal surgery) and complications such as renal impairment, infection, pulmonary

oedema and myocardial infarction. Such a study should be designed to show non-inferiority for crystalloid versus colloid.

8 Intravenous fluid therapy for routine maintenance

8.1 Introduction

Intravenous fluid therapy for routine maintenance refers to the provision of IV fluids and electrolytes for patients who cannot meet their needs by oral or enteral routes, yet are otherwise well in terms of fluid and electrolyte balance and handling (i.e. they are essentially euvolaemic with no significant electrolyte deficits, ongoing abnormal losses or complex internal redistribution issues). However, even when prescribing IV fluids for more complex cases, there is still a need to account for patients' routine maintenance requirements, providing IV fluid maintenance prescriptions that are then adjusted to account for their more complex fluid or electrolyte problems. Estimates of routine maintenance requirements are therefore essential for any patient on continuing IV fluid therapy.

The use of IV fluids for purely routine maintenance purposes is relatively unusual. Examples include patients following a dysphagic stroke, patients with GI obstruction before surgery, and other pre-operative patients who need to be nil-by-mouth. Occasionally IV fluids may also be needed for patients who are unable to access drinks because of physical debility, reduced mental capacity or diminished level of consciousness but in many of these cases, and indeed in some of the other instances mentioned above, it is often possible to meet fluid and electrolyte needs via enteral tubes or, occasionally, by using sub-cutaneous fluids.

8.1.1 Routine maintenance fluids for surgical patients

One group that frequently receives IV fluids which are essentially for 'routine maintenance' is post-operative patients, although early after surgery many such patients have fluid redistribution issues and either deficits or more frequently excesses consequent to imbalances in fluid and electrolyte loss vs. provision during the operation itself. Advances in surgery, anaesthesia and peri-operative care, however, have reduced the length of time that patients need to be nil by mouth (NBM) both prior to and following surgery and so even after major abdominal operations, gastrointestinal function returns rapidly. Early post-operative oral intake is often therefore possible and the absence of bowel sounds per se does not mean that food and drink will not be tolerated. Generally, Nasogastric (NG) tubes are only indicated for drainage in the presence of true ileus or gastric dysfunction (e.g. delayed gastric emptying after pancreatic surgery) and indeed, in many cases, morbidity from NG tubes may exceed benefit. Certainly, in the past, a combination of NG tubes and excess IV fluids may well have caused unnecessary delay in re-establishing oral intake and consequent prolonged length of stay and, even today, prolonged and often excessive post-operative IV maintenance fluids continue to be given in some hospitals.

The aim when giving routine maintenance fluids is to provide enough fluid and electrolytes to meet insensible losses (500-1000 ml), maintain normal status of body fluid compartments and enable renal excretion of waste products (500-1500 ml.). Routine maintenance provision should nearly always be a short-term measure since inappropriate therapy risks volume overload and electrolyte and acid-base disturbance particularly hyponatraemia. There may also be problems related to prolonged venous access.

Junior medical staff are more likely than senior staff to continue IV maintenance therapy when no longer required, rather than re-instigating oral intake. They are also less likely to initiate NG or parenteral feeding which help with risks of malnutrition as well as IV fluid problems. More senior involvement in IV fluid prescribing and feeding decisions is therefore needed.

8.1.2 Choice of intravenous fluids for maintenance

A variety of fluids can be used to meet routine maintenance needs although there is considerable debate about the optimal ones to use. See Table P.1 in Appendix P for the composition of some crystalloids commonly used in the UK.

Healthcare professionals involved in IV fluid prescribing should be familiar with the composition of the fluids they use, and it is the differing composition of these fluids (and their consequent differing properties) that underlie the debates about the best type of fluid to use and hence the evidence reviews undertaken for this Chapter.

Isotonic saline

Sodium chloride 0.9%, with or without additional potassium, is one of the most commonly used IV fluids in UK practice. It is distributed throughout the extracellular fluid compartment (ECF) with perhaps only 25% of the infused volume remaining in the intravascular compartment. In recent years, questions have been raised as to whether it is suitable for routine maintenance purposes since the high sodium content could promote a degree of unnecessary sodium and water retention and the high chloride content will promote some degree of hyperchloraemia. This may then lead to hyperchloraemic acidosis and/or significant reductions in renal blood flow and glomerular filtration rate as well as gastrointestinal mucosal acidosis and ileus . The use of 0.9% sodium chloride might therefore be better confined to resuscitation (this question is examined in chapter 4) or replacement of specific GI fluid or renal losses high in sodium chloride (examined in Chapter 5).

Glucose 5% solution

Glucose 5% solution provides a useful means of giving free water for, once the glucose is metabolised, the fluid is distributed throughout total body water. It is therefore a potentially useful means of correcting or preventing simple dehydration and the glucose content will also help to prevent starvation ketosis, although it is important to recognize that it will not make much of a contribution to covering a patients overall nutritional needs. The use of 5% glucose, , will increase risks of significant hyponatraemia, particularly in children, the elderly, patients on diuretics and those with excess ADH due to osmotic and non osmotic stimuli (a problem seen quite frequently in hospitalized patients). Nevertheless, hyponatremia is likely to be avoided by not exceeding recommended volumes of maintenance IV fluids and by careful monitoring of patients' clinical volume status and electrolyte measurements. Use of glucose containing solutions may also lead to hyperglycaemia in patients who are glucose intolerant, although this can be avoided or treated if patients are monitored appropriately.

Glucose salines

There are many different IV fluids containing glucose and saline in different concentrations but the two most commonly used in general areas of UK hospital practice are glucose 4% with sodium chloride (either 0.18% or 0.45%) . Both are available with or without potassium at various concentrations). The use of glucose 4% with sodium chloride 0.18% or even glucose 4% with sodium chloride 0.45% will promote hyponatraemia if given rapidly or in excess, although both are less likely to cause this than glucose 5% alone.

Balanced crystalloid solutions

Balanced crystalloids are distributed throughout the ECF and therefore have similar properties to sodium chloride 0.9% in terms of plasma volume expansion and overall fluid distribution. However, they have theoretical advantages over sodium chloride 0.9% in that they contain somewhat less sodium and

significantly less chloride. They may therefore cause less sodium and water retention than 0.9% sodium chloride as well as less hyperchloraemia and they do already contain other electrolytes in amounts which may meet overall maintenance needs.

A number of newer balanced crystalloid solutions are likely to appear on the market, better tailored to meet the theoretical requirements for maintenance. When prescribing these fluids it will be is essential to specify the 'Maintenance' version where appropriate since there may be other versions of the fluids designed for Resuscitation of Replacement. The fact that some balanced solutions contain lactate or other buffers is not likely to alter their usefulness for routine maintenance.

The evidence reviews described below examine the issues related to different types of potential routine maintenance fluids as well issues of the optimal volumes and timings to use. However, even before that evidence was explored, the GDG were aware that it would be difficult to interpret since most studies in this area vary at least two of these parameters simultaneously i.e. study arms in many RCTs differ in both volume given as well as type of fluid provided.

The GDG were also aware that most studies would be in post-surgical patients who in many ways are not a simple IV maintenance group. Many post-operative patients start with some degree of sodium and water excess due to intra-operative IV fluid provision when vasodilatation from anaesthesia, coupled with increased transcapillary escape from the stress responses to surgery (see section 5.1.2.3), often demands the infusion of considerable fluid volumes to maintain intravascular filling. Much of this fluid then migrates to the interstitial space and needs to be excreted during the early days after the operation and, furthermore, the stress responses triggered by the surgery are often still present to some degree during that period. Evidence from post-surgical studies may therefore have limited applicability to non-surgical 'pure maintenance' patients (in whom it is unlikely that studies have been performed) and studies commenced or undertaken before, during or very shortly after surgery are likely to be inapplicable.

8.2 Fluid types, volumes and timings for IV fluid maintenance

The GDG were interested in exploring any evidence which would identify the most clinical and cost effective fluid types for meeting routine fluid maintenance needs, as well as the best volumes, infusion rates and timing of delivery of those fluids.

8.2.1 Clinical evidence: Fluid types

Review question: What is the most clinical and cost effective fluid to be used for intravenous fluid therapy for routine maintenance in hospitalised patients?

We searched for randomised controlled trials comparing the effectiveness of giving equal volumes of different crystalloids for improving outcomes in hospitalised patients prescribed IV fluids for predominantly maintenance purposes. We looked for studies that compared the effectiveness of any of the following crystalloids, either alone or in combination: sodium chloride 0.9%, buffered or physiological solutions, sodium chloride 0.45% in glucose 5%, sodium chloride 0.18% in glucose 4%, alternate balanced solutions (see section 13 for definition) and glucose 5%.

For full details see review protocol in section C.4, Appendix C.

No RCTs were found comparing the same volumes of these different fluids for maintenance regimens in hospitalised patients.

See section 8.5 for linking evidence to recommendations

8.2.2 Clinical evidence: Volumes of IV fluids for maintenance

Review question: What is clinical and cost effectiveness of different volumes of fluid administration in patients requiring intravenous fluids for routine maintenance?

The objective of this review was to find out whether factors such as total volume (ml/kg/day) and whether giving fluids continuously over 24 hours vs. intermittently affect the safety and efficacy of maintenance fluid management.

We searched for RCTs comparing the effectiveness of varying different volumes between treatment arms, although in doing so it was inevitable that the resulting fluid regimens in different arms would also vary in electrolyte delivery as well as volume. Since pathophysiological changes during surgery mean that the intraoperative fluid is not really being given for maintenance alone, we only included studies where allocation to different IV fluid treatment arms commenced after operation. For more details see review protocol in section C.4, Appendix C. Four RCTs [35,55,63,114] comparing the safety and efficacy of restricted versus standard or liberal fluid management after surgery were identified. No RCTs in medical (non-surgical) populations were found. Since the four included studies varied in terms of the study populations and fluid strategies, they could not be pooled for analysis. Table 34 summarises the key population and intervention characteristics for each study. For further details of the included studies, see the evidence tables in section E. 4, Appendix E.

The list of excluded studies and reasons for exclusions are shown in section H.4, Appendix H.

Table 34: Summary of key populations and intervention characteristics

Study ID	Population	Restricted	Standard	Other information
GONZALEZ-FAJARDO 2009[35]	Open abdominal vascular surgery 24 hours post-operatively N=40	Sodium chloride 0.9%, 1.5 litres	1.5 litres of sodium chloride 0.9% and 1 litre of Glucose 5%	Oral fluids started on 3rd day About 6 litres excess during operation/ICU 40mmol potassium/day
LOBO 2002[55]	Hemi-colectomies & sigmoid colectomies for cancer N=20	≤2L IV fluid, 0.5 litre of sodium chloride 0.9% and 1.5 litres of glucose 5% Or 2 litres of Glucose 4% / sodium chloride 0.18% (≤27ml/kg/day)	≥3 litres IV fluid, 1 litre of sodium chloride 0.9% And 2 litres of glucose 5% (≥43ml/kg/day)	Oral fluids encouraged post-surgery More oral fluids intake recorded in restricted group 40-60mmol potassium/day
MACKAY 2006[63]	Colorectal surgery with primary anastomosis N=80	2 litres of glucose 4% / sodium chloride 0.18%	2 litres of glucose 5% and 1 litre of sodium chloride 0.9%	Oral fluids encouraged post surgery IV fluid until day 3
VERMEULEN2009[114]	General abdominal surgery N=62	0.5 litre of glucose 5% and 1 litre of sodium chloride 0.9% (21ml/kg/day)	1 litre of glucose 5% and 1.5 litres of sodium chloride 0.9% (33ml/kg/day)	Immediately post surgery, 1.5 litres and 2.5 litres /24 hour for restricted and standard group

Table 35: Clinical evidence profile: Restricted versus standard volumes of intravenous maintenance fluids

Quality assessment							Number of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Restricted volume	Standard volume	Relative (95% CI)	Absolute		
All cause mortality (up to 30 days) (follow-up 30 days)[35,55,63,114]												
4	RCTs	No serious risk of bias	Serious(a)	Serious(b)	No serious imprecision	None	99	103	Not pooled- See Table 36		LOW	CRITICAL
Respiratory failure (follow-up 30 days)[35,55,63,114]												
4	RCTs	Serious(c)	Serious(a)	Serious(b)	Very serious(d)	None	99	103	Not pooled – See Table 37		VERY LOW	IMPORTANT
Development of renal failure/AKI (follow-up 30 days)[35,63,114]												
3	RCTs	Serious(c)	Serious(a)	Serious(b)	Very serious(d)	None	89	93	Not pooled – See Table 38		VERY LOW	IMPORTANT
Quality of life (measured with SF 36, at 3 months)[63]												
1	RCTs	Serious(e)	None	Serious(b)	Very serious(f)	None	25	36	No significant difference (f)		VERY LOW	IMPORTANT
Length of hospital stay (post operative)[35,55,63,114]												
4	RCTs	Serious(e)	Serious(a)	Serious(b)	Serious(g)	None	99	103	Not pooled- See Table 39		VERY LOW	IMPORTANT
Morbidity (SOFA score)– not reported												

(a) There was important clinical heterogeneity between studies, including; different volumes of fluids used in "liberal" and "restricted" arms, patient's fluid status at the start of study (patients in one study had severe overload17), patient populations, and magnitude of difference in between "liberal" and "restricted" strategies. Direction of effect dependent of whether fluid strategy promotes fluid balance in the studies, rather than "liberal" or "restricted". Direction of effect different between studies. Results not pooled.
(b) The evidence were from abdominal surgical patients with restricted vs standard volumes started immediately post surgery; except for one study, which recruited post abdominal vascular surgery patients 17. It is unclear if this evidence is directly applicable to maintenance patients - the fluid handling in these patients may be different from the general (medical) patient.
(c) Outcomes were not clearly defined for development of renal failure in studies. Variations in reporting of respiratory problems, ranging from "respiratory failure" to "infection".
(d) Event rates were low and overall pooled number of participants was low. Confidence intervals were wide and crossed MIDs.
(e) Only one study was double blinded but had a high rate of unblinding or deviation from protocol4. One study was open label – actual IV fluid prescription were dependent on investigator (for study arm) and surgical team members (for control arm) 2. The other studies were observer blinded 1;3. .
(f) Sample size may not be powered to detect a difference. Actual values not reported.
(g) One study favoured standard, while the others favour restricted, or showed no difference. Results not pooled due to different populations

Table 36: All cause mortality

Study ID	Restricted volume Events/total (%)	Standard volume Events/total (%)	Relative risk (95% CI)
GONZALEZ-FAJARDO2009[35]	0/20 (0%)	1/20 (5%)	0.33 [0.01, 7.72]
LOBO2002[55]	0/10 (0%)	1/10 (10%)	0.33 [0.02, 7.32]
MACKAY2006[63]	1/39 (2.6%)	1/41 (2.4%)	1.05 [0.07, 16.23]
VERMEULEN2009[114]	1/30 (3.3%)	1/32 (3.1%)	1.07 [0.07, 16.30]

Table 37: Development of respiratory complications

Study ID	Restricted volume Events/total (%)	Standard volume Events/total (%)	Relative risk (95% CI)
GONZALEZ-FAJARDO2009[35]	0/20 (0%)	1/20 (5%) (pulmonary oedema)	0.33 [0.01, 7.72]
LOBO2002[55]	0/10 (0%)	2/10 (20%) (respiratory infection)	0.20 [0.01, 3.70]
MACKAY2006[63]	Unclear(a)	Unclear(a)	Not estimable
VERMEULEN2009[114]	1/30 (3.3%) (respiratory disorder or infection)	0/32 (0%)	3.19 [0.14, 75.49]

(a) Study states that one person died of respiratory failure. Does not state which group. Already accounted for in all-cause mortality analysis.

Table 38: Development of renal failure or AKI

Study ID	Restricted volume Events/total (%)	Standard volume Events/total (%)	Relative risk (95% CI)
GONZALEZ-FAJARDO2009[35]	0/20 (0%)	0/20 (0%)	Not estimable
MACKAY2006[63]	0/39 (0%)	0/41 (0%)	Not estimable
VERMEULEN2009[114]	0/30 (0%)	0/32 (0%)	Not estimable

Table 39: Length of hospital stay (days)

Study ID	Restricted volume	Standard volume	p value / effect size
GONZALEZ-FAJARDO2009[35]	Post-operative stay including ICU: Mean 8.4 (95% CI: 7.6 - 9.1) n=20	Post-operative stay including ICU: Mean 12.4 (95%CI: 8.7 - 16.1) n=20	0.003 (reported, unclear which test used)
LOBO2002[55]	Post-operative stay: Median 6.0 (IQR 5.0–7·0) n=10	Post-operative stay: Median 9.0 (IQR 7.8-14.3) n=10	0.001 (reported, using Mann Whitney U test)
MACKAY2006[63]	Median 7.2 (IQR 6·1–11·0) n=39	Median 7.2 (IQR 6·1–11·2) n=41	0.902 (reported, log rank test) Hazard ratio: 1.03 (0.66, 1.61)
VERMEULEN2009[114]	Median 9.0 (IQR 6.8 -11.3) n=30 [Mean 12.3 (SD 12.7)]	Median 7.0(IQR 6.0-9.8) n=32 [Mean 8.3 (SD 4.5)]	0.049 (reported, Mann Whitney U test)

8.2.3 Clinical evidence: Timing of IV fluid maintenance

Review question: What are the most clinical and cost effective timings of administration of intravenous fluids in patients requiring intravenous fluids for routine maintenance?

The objective of this review was to find out whether factors such as when fluid should be initiated or rate of administration (ml/kg/hour) would affect the safety and efficacy of maintenance fluid management.

We searched for RCTs comparing the effectiveness of varying timings or rate of fluid administration between treatment arms. For more details see review protocol in section C.4, Appendix C.

No evidence was found comparing different timings or rates of IV fluid maintenance administration.

8.3 Economic evidence

No published studies of cost-effectiveness were found. The GDG considered the choice of maintenance therapy to be a high priority for de novo economic modelling. However, the clinical review did not find evidence of the relative clinical effectiveness of different fluid types, so a simple cost analysis was conducted with a threshold sensitivity analysis around the number of complications averted, see Appendix N.

It was assumed that administration costs would be similar for each fluid and therefore only fluid costs and complication costs were included. Fluid costs were provided by the NHS Commercial Medicines Unit (CMU), where possible. For a few fluids, a cost was not available from the CMU, so these were provided by the Trusts of individual GDG members.

The cost of a major fluid-related complication (see 4.2.3) was estimated using NHS reference costs to be £1,868 (or £3,000 including a critical care episode).

The cost of each fluid is shown in Table 40 along with the number of complications that would need to be averted to make each fluid cost neutral. The cheapest fluids cost £7.00 per patient over 5 days – see Table. The lowest cost treatment that met bodily fluid requirements (see 5.1, especially Table 9), was Sodium chloride 0.18% in 4% glucose + Potassium (2G/27mmol, 0.2 % concentration)at £12.50 per patient, which would have to avert only 2-3 major complications per 1000 patients to be cost neutral. The most expensive fluid cost £108 and would need to avert 34-54 complications per 1000 patients to be cost neutral.

This analysis can be considered as partially applicable (since NHS unit costs were used but QALYs were not estimated) but it has potentially serious limitations since some of the fluid costs were taken from an individual Trust and therefore aren't necessarily generalizable. Furthermore, conclusions about cost-effectiveness or cost neutrality are not possible without evidence of the number of complications averted due to monitoring.

Table 40: Cost of maintenance fluids

IV fluid type (in order of cost of fluid per patient) [2]	Cost of fluid per 70kg patient (2000ml per day for 5 days) [1]	Number of extra complications per 1000 patients that would need to be averted for fluid to the lowest cost fluid (including critical care)
0.9% sodium chloride	£7.00	-
Sodium chloride 0.18% in 4% glucose	£7.00	-
5% Glucose	£7.00	-
1Lx 0.9% sodium chloride to 2Lx 5% glucose	£7.00	-
Hartmann's Solution	£8.50	1 (1)
Alternate Balanced Solution	£9.00	1 (1)
1Lx Hartmann's to 1.5Lx 5% Glucose with Potassium (3G/40mmol)	£9.88	2 (1)
Sodium chloride 0.18% in 4% glucose + Potassium (2G/27mmol)	£12.50	3 (2)
5% Glucose with potassium (2G/27mmol)	£14.64	4 (3)
1Lx 0.9% sodium chloride to 2Lx 5% Glucose with Potassium (2G/27mmol)	£14.78	4 (3)
0.9% Sodium Chloride with potassium(2G/27mmol)	£15.12	4 (3)
1Lx Ringers to 1.5Lx 5% Glucose with Potassium (3G/40mmol)	£16.48	5 (3)
0.45% Sodium Chloride in 5% glucose	£24.00	9 (6)
Ringers Lactate	£25.00	10 (6)
2Lx 0.45% sodium chloride in 5% Glucose with potassium to 0.5Lx 0.45% sodium chloride in 5% Glucose	£108.16	54 (34)

8.4 Evidence statements

8.4.1 Clinical

8.4.1.1 Fluid types for maintenance

No studies were found comparing the effectiveness of the same volumes of different crystalloids for hospital patients needing IV fluids for routine maintenance.

8.4.1.2 Fluid volumes for maintenance - narrative summary

Four RCTs were found that compared the safety and effectiveness of a "restricted" vs "standard" (or "liberal") fluid strategy in 202 people undergoing surgery.

Critical outcomes:

All cause mortality

Two RCTs suggested that restricted fluid regimens may be associated with lower all cause mortality compared to liberal intravenous fluid strategies, although the restricted regimens also delivered less electrolytes particularly less sodium chloride. Two further RCTs suggested that there is no difference in all cause mortality between groups, although in all studies, the direction of effect is uncertain since event rates were low. All evidence is of very low quality.

Important outcomes:

Development of respiratory complications

The direction of effect in terms of developing respiratory complications is unclear. Two RCTs suggested that restricted fluid regimens may be associated with lower respiratory complications (in people undergoing abdominal vascular surgery and colon resections) but one RCT suggested that standard volume regimens may have lower rates of respiratory complications. A further RCT mentioned occurrence of respiratory failure but did not state in which group. The event rates were low for all studies and all evidence is of very low quality.

Development of renal failure or acute kidney injury

All four RCTs suggested that there was no clinically important difference in the risks of developing renal failure or acute kidney injury when comparing patients receiving restricted IV fluids compared to those receiving standard fluid volumes with no reports of renal failure or acute kidney injury in either group for any of the studies. All evidence is of very low quality.

Outcome: Quality of life

In terms of quality of life assessed by SF-36, one RCT indicates there is no difference between standard or restricted IV fluid administration at 3 months. However the effect size could not be determined and no clear interpretation can be made from this evidence which was very low quality.

Outcome: Length of hospital stay

The direction of effect on lengths of hospital stay were variable. Two RCTs suggested that restricted fluid regimens may be associated with shorter hospital stays (in people undergoing abdominal vascular surgery and colon resections) but one RCT suggested that restricted volume may lead to longer hospital stays, and another reported no difference between groups. The overall effect is therefore uncertain especially as results could not be pooled but the differences in the direction of effect can be explained by variation in the degree of fluid restriction imposed in different studies (see section 8.5 below). All evidence is of very low quality.

Outcome: Morbidity

No studies reporting morbidity data as measured by SOFA scores were found.

8.4.1.3 Fluid timings

No studies were found comparing the effectiveness of any of the crystalloids for use in intravenous maintenance regimens in hospitalised patients.

8.4.2 Economic

An original comparative cost analysis showed that:

- The lowest cost fluids were sodium chloride 0.9%, sodium chloride 0.18% in glucose 4%, glucose 5% at £7.00 per patient over 5 days.
- Sodium chloride 0.18% in glucose 4% + Potassium (2G/27mmol, 0.2 % concentration)at £12.50 per patient, would have to avert only 1-2 major complication per 1000 patients to be cost neutral compared with the lowest cost fluids.
- The most expensive fluid cost £108 and would need to avert 34-54 complications per 1000 patients to be cost neutral.
- Other fluids would have to avert up to 10 complications per 1000 patients to be cost neutral.

This analysis was assessed as partially applicable with potentially serious limitations.

8.5 Recommendations and link to evidence

Recommendations	**19. If patients need IV fluids for routine maintenance alone, restrict the initial prescription to:** • **25–30 ml/kg/day of water and** • **approximately 1 mmol/kg/day of potassium, sodium and chloride and** • **approximately 50–100 g/day of glucose to limit starvation ketosis. (This quantity will not address patients' nutritional needs; see Nutrition support in adults [NICE clinical guideline 32].)** **For more information see IV fluid prescription (by body weight) for routine maintenance over a 24-hour period.** **20. For patients who are obese, adjust the IV fluid prescription to their ideal body weight. Use lower range volumes per kg (patients rarely need more than a total of 3 litres of fluid per day) and seek expert help if their BMI is more than 40 kg/m^2.** **21. Consider prescribing less fluid (for example, 20–25 ml/kg/day fluid) for patients who:** • **are older or frail** • **have renal impairment or cardiac failure** • **are malnourished and at risk of refeeding syndrome (see Nutrition**

	support in adults [NICE clinical guideline 32]). **22. Consider delivering IV fluids for routine maintenance during daytime hours to promote sleep and wellbeing.**
Relative values of different outcomes	The GDG were interested in all cause mortality, length of hospital stay and complications including renal, respiratory and morbidity as measured by SOFA or MODS scores. All cause mortality was considered to be the most important outcome for decision making, although all other outcomes were deemed as important for informing recommendations.
Trade off between clinical benefits and harms	it is unclear from the clinical evidence whether mortality or morbidity in terms of respiratory problems, AKI or any scoring systems are improved by restricted fluid volumes compared to standard volumes. , However, there did appear to be significant effects on length of hospital stay in three out of four of the studies although two suggested reductions when restricted volume regimens were used compared to standard volumes whilst one suggested the reverse. However, the differences in direction of the effect can probably be explained by the different degree of fluid restriction in the different studies (see Quality of Evidence below). The studies included in the review weighed patients daily and patients receiving higher volumes of fluids showed weight gain, which is likely to be associated with excessive fluid provision.
Economic considerations	No published health economic evidence was identified. However, the GDG would expect that restricting fluid intake would be cost saving as well as health improving, since not only will less fluid cost less but there would be lower treatment costs from the costs of treating the complications associated with fluid overload. As noted above the impact of restricting fluids on length of stay is uncertain.
Quality of evidence	No RCT evidence was found comparing the fluid maintenance types of interest to the GDG. No studies comparing the effect of different timings of starting, stopping or duration of IV fluid administration were found. The GDG discussed the following in relation to the quality of the evidence related to the optimal volume of infusion for routine maintenance : • The studies found had small sample sizes (imprecision). • There were limitations in study design and conduct which led to risk of bias and downgrading within the GRADE quality criteria. • The studies included had post-operative patient samples (abdominal surgery or abdominal vascular study) with none found relating to medical patients. The GDG therefore discussed the extent to which findings could be extrapolated to all patients requiring maintenance therapy. The population in the study was indirect to the target review population. Post surgical patients are not thought to be typical of those patients receiving maintenance fluids. This is because surgical patients do often have excess fluid loads and the nature of the procedure means that they retain fluids. [82] • There was wide variation in study protocols and the degree of difference between what was considered to be restricted and standard provision. For example, in the Mackay study, the differences in fluid volumes between the two regimens were not clinically significant and the differences in weight gain observed between the standard and restricted groups was less than 1kg, which would not be considered

	clinically significant. It was noted that not only the fluid volume but the sodium chloride provision was very different across the four studies identified which prevented meaningful meta-analysis. The restricted groups were given fluid volumes ranging from 1.5L to 2.5 L with sodium chloride provision ranging from 62 mmols to 231 mmols, while the standard regimen groups in the studies received fluid volumes between 2L and more than 4 L of fluid with sodium chloride provision ranging from 154 mmol to and 231 mmol. GDG felt that these differences might explain the differences in the results with potentially adverse outcomes seen with either too much or too little fluid and sodium chloride and that this would be logical in terms of fluid prescribing principles.
Other considerations	The GDG took into consideration many other studies, which did not meet the criteria of the review but which had been used to inform clinical opinion over many years. **Fluid type** • No separate evidence was found relating to the best type of fluid for the management of people requiring fluid maintenance but all of the studies reviewed used either glucose 4%, sodium chloride 0.18% or a combination of glucose 5% and sodium chloride 0.9%.A consensus recommendation was therefore made based on GDG opinion and experience. • The GDG noted that the use of glucose saline, particularly Sodium chloride 0.18%/4% glucose could predispose to the development of hyponatraemia but they agreed that the cause of this complication is multifactorial and is particularly a consequence of of administering excessive volumes especially when there are other sources of water provision (e.g. from IV medication or oral routes) or the presence excess anti diuretic hormone (ADH) due to non osmotic stimuli which does occur in some hospital patients. The complication should therefore be avoided if only moderate volumes of IV fluids are prescribed for maintenance and patients are adequately monitored, with the development of hyponatraemia prompting a clinical review of volume status and a change in infusion fluids (although hyponatraemia in the context of oedema should prompt senior review since many of these patients have both sodium and water overload and the best treatment is fluid restriction rather than additional sodium chloride administration. The use of glucose containing solutions may lead to hyperglycemia in patients who are glucose intolerant. Blood glucose monitoring should be part of assessments of patients receiving glucose containing fluids in general. Patients with diabetes are outside the scope of this guideline). **Commencement of oral or enteral fluids** The GDG were interested in identifying the best time to cease IV fluid management since they were aware, from their clinical experience, that prolonged IV fluid management can lead to significant problems and increased hospital stay. No direct evidence was found to answer this question but there have been Cochrane reviews looking at oral and enteral feeding which compare early commencement of feeds to delayed commencement. These reviews conclude that patients receiving early oral or enteral feeding have reduced lengths of stay. The GDG surmised that if patients can tolerate food, they are able to tolerate oral fluids and hence that these findings support the consensus recommendation that IV fluids should be stopped as soon as a patients can tolerate fluids by other routes. **Restricted compared to standard volumes** The GDG considered the volume of fluids to be a central aspect in fluid maintenance management. Adverse events from fluid management are related to patients being given inappropriate amounts of fluids and electrolytes (either too much or too little. The GDG agreed that it was difficult to interpret the results based on the limitations of the studies and variation in effect (see above). As such, they agreed on an

	appropriate range that should be given (including the amount of sodium, potassium and chloride). The GDG also considered that there are groups of patients who should receive lower volumes in the ranges recommended. For example, obese individuals do not have the same metabolic or muscle mass as people with lean body mass. Oedematous patients require special consideration also, in that the additional fluid must be taken into account before prescribing the volume. It was highlighted that whilst the recommendation is to measure fluid volume required in terms of millilitre per kilogram of body weight, fluid bags are prescribed by the litre. See section P.4, Appendix P for table to aid rapid calculation of suggested volumes. **Fluid prescribing during daytime hours** • The GDG discussed that adequate sleep at night is crucial to patient recovery. While it was acknowledged that there may be instances where intravenous fluid therapy for routine maintenance may have to be given at night due to competing demands during the day, the aim should be to promote sleep and well-being for a complete recovery. The GDG also considered the implications of this recommendation to the effect of doctors requiring a clinical indication to restart the fluids which will lead to reduced inappropriate IV fluid prescribing, reduced work for nursing staff at night and improved patient mobility due to not being tied to a drip. **Other considerations** • Clinical evaluation and continued monitoring is important to ensure that patients are receiving the correct volume and type of fluid. • The GDG discussed how body weight is defined i.e. actual or lean • Research recommendations – the GDG agreed that there is a need for research related to IV fluid routine maintenance provision in medical patients but recognised that there could be difficulties in designing such a trial. • Recommendation 22 was identified as a key priority for implementation by the GDG.

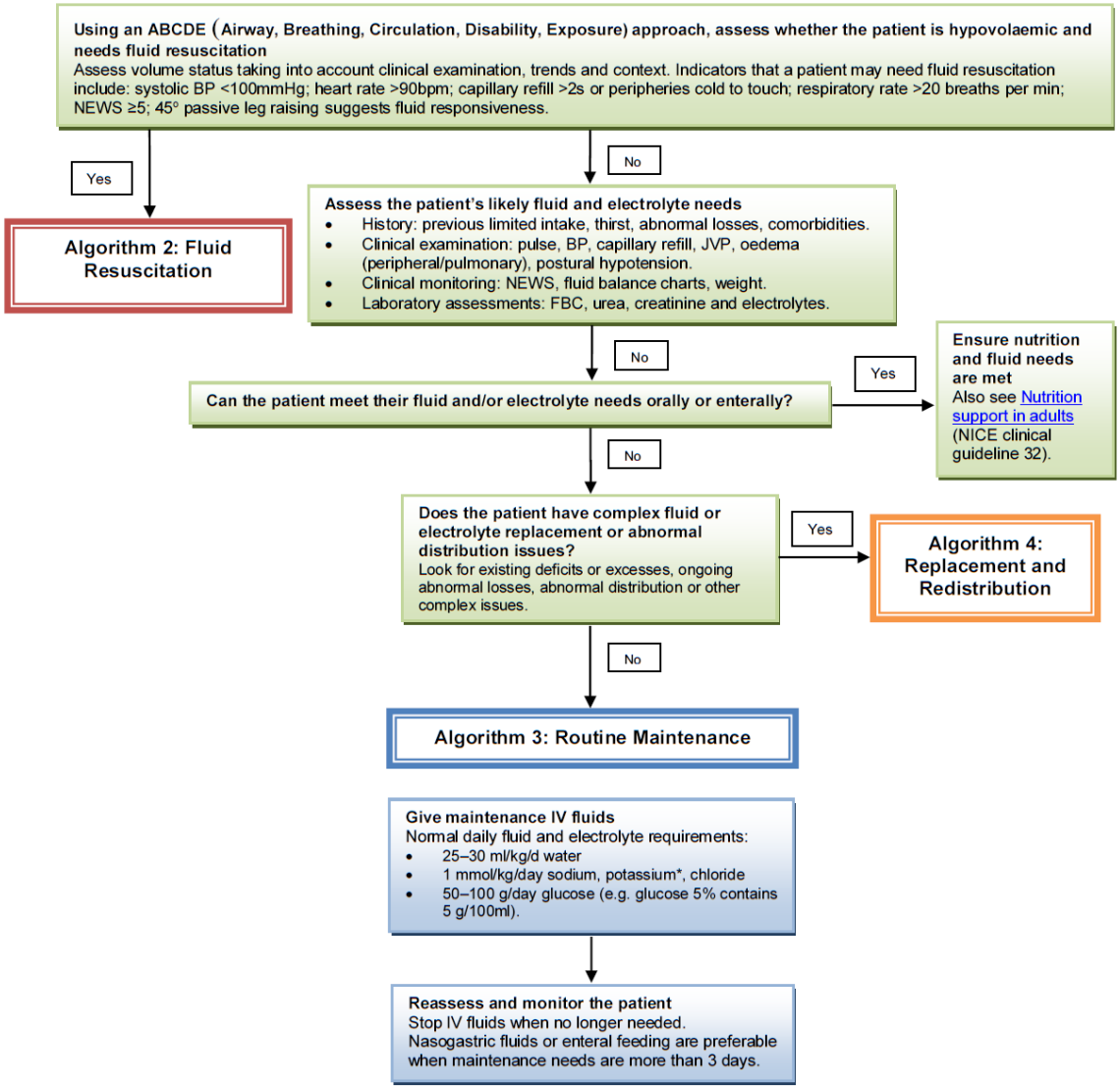
Recommendations	**23. When prescribing for routine maintenance alone, consider using 25–30 ml/kg/day sodium chloride 0.18% in 4% glucose with 27 mmol/l potassium on day 1 (there are other regimens to achieve this). Prescribing more than 2.5 litres per day increases the risk of hyponatraemia. These are initial prescriptions and further prescriptions should be guided by monitoring.**
Relative values of different outcomes	The GDG considered all cause mortality to be the most important outcome. Other outcome considered important for decision making included development of renal complications and respiratory complications. However, no evidence was identified for any of these outcomes.
Trade off between clinical benefits and harms	Use of sodium chloride 0.18% in Glucose 4% was agreed to be a simple and effective regimen for routine maintenance. However it was recognised that there is a risk of hyponatremia and hyperglycemia and this should be kept in mind when prescribing.
Economic considerations	There were no published cost-effectiveness studies found. An original cost analysis compared a number of different fluid strategies, some of which included potassium and others did not. The lowest cost fluids were 0.9% sodium chloride, Sodium chloride 0.18% in 4%

	glucose, 5% glucose at £7.00 per patient over 5 days. However, the GDG do not believe that this strategy would effectively meet bodily requirements. The lowest cost treatment strategy that would meet bodily maintenance fluid requirements was found to be Sodium chloride 0.18% in 4% glucose + potassium (2G/27mmol, 0.2 % concentration). At a cost of £12.50 per patient, it would have to avert only 2-3 major complications per 1000 patients to be cost neutral compared with the lowest cost fluid, which the GDG considered plausible. The GDG did not want to be too prescriptive about the type of fluid used on the basis that: • the price of fluids varies considerably according to local contracts and volumes purchased; • manufacturers may decide to introduce new brands of fluids as a result of this guideline. If this guideline leads to a standardisation of practice then the cost of such fluids are likely to come down. Trusts should purchase for maintenance the lowest cost fluid that meets the daily requirements recommended in this guideline.
Quality of evidence	No RCT evidence was found comparing the different types of fluid for routine maintenance. The recommendations are therefore based on the consensus opinion of the GDG members.
Other considerations	The GDG discussed that the commonly used maintenance regimens were not appropriate and although these were included in the comparators, they were not acceptable. The GDG discussed that for simplicity of administration, the IV fluid regimens containing only one fluid (that is Sodium chloride 0.9% or Glucose 5%) were most acceptable and the cost of each would also have to be taken into account. The GDG discussed recommending Sodium chloride 0.18% in Glucose 4% as a maintenance regimen. It was highlighted that a recent MHRA warning had been issued against the use of this fluid in children under 16 years due to resulting fatal hyponatremia. The GDG agreed that the recommendation should acknowledge this warning, but equally, it was to be made clear that this recommendation was for maintenance use and not for use during resuscitation or in paediatric patients. It was also decided that a warning should accompany this recommendation stating that caution was needed in patients with low sodium levels and hyponatremia should be checked for in all cases with adjustment of the prescription accordingly. The recommendation above is for the initial prescription. The GDG also discussed that this recommendation would have to be practiced in conjunction with appropriate assessment and monitoring as this was essential if the benefits were to be observed. Due to the paucity of evidence in this topic area, the GDG prioritised a research recommendation evaluating the reduction in risk of hyponatraemia with higher sodium containing IV fluid regimens for maintenance (see section 8.6).

8.5.1 Algorithm 3: Routine maintenance

NICE National Institute for Health and Care Excellence

Algorithms for IV fluid therapy in adults


Using an ABCDE (Airway, Breathing, Circulation, Disability, Exposure) approach, assess whether the patient is hypovolaemic and needs fluid resuscitation
Assess volume status taking into account clinical examination, trends and context. Indicators that a patient may need fluid resuscitation include: systolic BP <100mmHg; heart rate >90bpm; capillary refill >2s or peripheries cold to touch; respiratory rate >20 breaths per min; NEWS ≥5; 45° passive leg raising suggests fluid responsiveness.
Yes
No
Algorithm 2: Fluid Resuscitation
Assess the patient's likely fluid and electrolyte needs
History: previous limited intake, thirst, abnormal losses, comorbidities.
Clinical examination: pulse, BP, capillary refill, JVP, oedema (peripheral/pulmonary), postural hypotension.
Clinical monitoring: NEWS, fluid balance charts, weight.
Laboratory assessments: FBC, urea, creatinine and electrolytes.
No
Can the patient meet their fluid and/or electrolyte needs orally or enterally?
Yes
Ensure nutrition and fluid needs are met
Also see Nutrition support in adults (NICE clinical guideline 32).
No
Does the patient have complex fluid or electrolyte replacement or abnormal distribution issues?
Look for existing deficits or excesses, ongoing abnormal losses, abnormal distribution or other complex issues.
Yes
Algorithm 4: Replacement and Redistribution
No
Algorithm 3: Routine Maintenance
Give maintenance IV fluids
Normal daily fluid and electrolyte requirements:
25–30 ml/kg/d water
1 mmol/kg/day sodium, potassium*, chloride
50–100 g/day glucose (e.g. glucose 5% contains 5 g/100ml).
Reassess and monitor the patient
Stop IV fluids when no longer needed.
Nasogastric fluids or enteral feeding are preferable when maintenance needs are more than 3 days.

* Weight-based potassium prescriptions should be rounded to the nearest common fluids available (for example, a 67 kg person should have fluids containing 20 mmol and 40 mmol of potassium in a 24-hour period). Potassium should not be added to intravenous fluid bags as this is dangerous.

'Intravenous fluid therapy in adults in hospital', NICE clinical guideline 174 (December 2013. Last update December 2016)

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This section links the evidence to Algorithm 3 and the recommendation bullet specific to routine maintenance.

Recommendations	**Offer IV fluid therapy as part of a protocol (see Algorithms for IV fluid therapy):** • **Assess patients' fluid and electrolyte needs following Algorithm 1: Assessment.** • **If patients need IV fluids for fluid resuscitation, follow Algorithm 2: Fluid resuscitation.** • **If patients need IV fluids for routine maintenance, follow Algorithm 3: Routine maintenance.** • **If patients need IV fluids to address existing deficits or excesses, ongoing abnormal losses or abnormal fluid distribution, follow Algorithm 4: Replacement and redistribution.**
Relative values of different outcomes	The GDG were interested in all cause mortality, length of hospital stay, complications including renal and respiratory problems, and morbidity as measured by Sequential Organ Failure Assessment (SOFA) scores. All cause mortality was considered to be the most important outcome for decision making, although all other outcomes were deemed as important for informing recommendations.
Trade off between clinical benefits and harms	The algorithm for routine maintenance was based on: • evidence based on the principles of fluid prescribing as described in section 5.1 • the reviews of the use of algorithms in fluid prescribing described in section 5.2 • guidance on the assessment of patients according to the NEWS score [95] • guidance on the non-fluid based elements recommended for resuscitation contained current Advanced Life Support guidance [5] • the evidence reviews informing the type, volume and timing of fluid administration for routine maintenance (see section 8.2) This approach allowed the GDG to develop the complete routine maintenance algorithm as well as some specific recommendations on IV fluid therapy for routine maintenance.
Economic considerations	In section 5.2.3 it was noted that for patients with sepsis, protocolised care was found to be cost-effective for sepsis patients in two studies and cost saving in a third study. Third evidence was considered to be partially applicable and with potentially serious limitations. There was no cost-effectiveness evidence for patients without sepsis. However, given that the health improvements observed in the review of clinical effectiveness evidence were just as pronounced for intra-operative care the GDG felt that the economic benefits of protocols are very likely to be achievable across all settings.
Quality of evidence	The algorithm was based on established guidance (NEWS, ALS guidance), consensus opinion of the GDG members and findings from the systematic reviews undertaken for determining the most clinical and cost-effective type, volume and timing of fluids to be used for routine maintenance and the review on clinical effectiveness of protocolised care. Quality of evidence for outcomes analysed in the systematic reviews ranged

	from very low to high.
Other considerations	Despite the paucity of evidence on the use of protocols for IV fluid administration (see section 5.2), the GDG felt that protocolised care in general achieves better outcomes for patients and therefore decided that an algorithmic approach to fluid resuscitation is appropriate in this context. In designing the algorithm, the GDG placed particular emphasis on developing recommendations that a foundation year doctor could follow via the protocol to initiate appropriate resuscitation treatment as a first responder. The recommendations and protocol contained within the algorithm on the type, volume, timing and rate of IV fluid use for routine maintenance are based on: •the principles of fluid prescribing described in section 5.1 •the reviews of evidence related to the use of algorithms in fluid prescribing described in section 5.2 •the evidence reviews on fluid type, volume, rate and timing presented here; and •the consensus expert views of the GDG. The GDG discussed the importance of stopping IV fluids as soon as possible with reference to the NICE guidance on nutrition support.[72] It was agreed that proper assessment and monitoring was and integral part of this algorithm and was essential if the benefits were to be observed. The choice of type of fluid was determined by the systematic reviews undertaken for type, volume and timing of routine maintenance. This recommendation was identified as a key priority for implementation by the GDG.

8.6 Research recommendations

5. Does a higher sodium content IV fluid regimen for maintenance reduce the risk of developing hyponatraemia and volume depletion without increasing the risk of volume overload in hospitalised adults?

Why this is important

Patients who cannot meet their daily needs of fluids and electrolytes through oral or enteral routes but are otherwise euvolaemic often need IV fluid therapy for maintenance. The most common complications of this therapy are hyponatraemia (if excessive IV water is administered), volume overload (if excessive sodium and water are administered) and volume depletion and/or acute kidney injury (if inadequate sodium and water are administered). There are no published trials considering what the optimal IV fluid regimen for maintenance is.

A randomised controlled trial is needed to compare IV fluid maintenance regimens with different sodium concentrations (for example, comparison between sodium chloride 0.18% in glucose 4% and sodium chloride 0.45% in glucose 4% solutions) in terms of the above detailed complication rates, cost and other clinical outcomes (for example, length of stay). The patient group will be heterogeneous, and analysis should consider subgroups of both 'medical' and 'surgical' patients.

9 Intravenous fluid therapy for replacement and redistribution

9.1 Introduction

Many patients who need intravenous fluids have specific needs to cover replacement of existing deficits or ongoing losses of fluid or electrolytes and/or problems of internal redistribution of fluid and electrolytes which must be accounted for when deciding on the optimal IV fluid prescription.

9.1.1 Principles of IV fluid prescribing for replacement of deficits or ongoing abnormal losses

Replacement intravenous fluid and electrolytes are needed to treat existing deficits or ongoing abnormal external losses, usually from the GI tract (e.g. ileostomies, fistulae, NG drainage and surgical drains) or urinary tract (e.g. when recovering from acute kidney injury). High insensible losses may also occur in patients with fever, and burns patients can lose enormous amounts of what can be effectively plasma. If patients do need intravenous fluids for replacement purposes, it is important to recognize that these will usually be in addition to fluids that meet their routine maintenance requirements.

Abnormal external fluid losses are seen in many circumstances as illustrated in the diagram of ongoing losses (see section 4.2.2) In general, IV fluid therapy prescribed for replacement should aim to meet the extra requirements for fluid and electrolytes as well as maintenance needs, so that homeostasis is restored and maintained. As usual, all sources of fluid and electrolyte intake must be allowed for (e.g. oral intake, enteral tube provision and fluids given with drugs) in tailoring the IV fluid prescription.

Although it is sometimes possible to measure both fluid volumes and electrolyte content of abnormal losses accurately (e.g. with high urinary loss), it is often only possible to estimate volumes and electrolyte contents, using the likely composition of different losses that are shown in the diagram of ongoing losses. Since these estimates may well be subject to wide errors, particularly close clinical and laboratory monitoring will be needed.

9.1.1.1 Choice of fluids in patients with replacement needs

Although beyond the scope of this guidance, replacement for blood loss is generally by the use of 0.9% sodium chloride, balanced crystalloids or suitable colloids (with packed red cells as necessary). The replacement for other losses e.g. GI or urinary, will usually depend on estimates of their composition but 0.9% sodium chloride, glucose 5% and glucose with saline solutions are all used (with or without additional potassium as appropriate) as are balanced crystalloid solutions. Colloids are not generally used in these patients unless their deficits are such that they need urgent resuscitation.

9.1.1.2 Rates of IV fluid infusion for patients with replacement needs

If patients with abnormal fluid or electrolyte losses develop significant deficits over prolonged periods, physiological adaptations and changes in ECF/ICF distribution may occur which allow the patient to function moderately well. Sudden correction of these abnormalities can then be associated with profound and even seriously damaging consequences (e.g. central pontine demyelinolysis when hyponatramia is corrected too swiftly). It is therefore best to reverse deficts cautiously over several days In situations where they have developed over days or weeks, unless there is a life threatening need for

fluid resuscitation or an urgent reason to correct plasma electrolyte values e.g. severe hypo- or hyperkalaemia.

9.1.2 Principles of IV fluid prescribing for patients with fluid redistribution/abnormal fluid handling problems

In addition to external losses, some hospital patients have significant internal redistribution of fluids especially those who are critically ill, those with sepsis, post-operative patients, patients with severe renal, liver or cardiac problems, and patients who are malnourished. Such patients often develop sodium and water excess (leading to pulmonary and peripheral oedema, weight gain, compartment syndrome and poor wound healing), which frequently occurs in the context of low intravascular volume (and associated low urine outputs) due to high trans-capillary escape. Furthermore, some patients sequester fluids in the intestinal tract, chest or peritoneal cavity.

Prescribing appropriate IV fluids for patients with redistribution type problems is particularly difficult since too little leads to intravascular hypovolaemia, low blood pressure, poor urine output and poor tissue perfusion, whilst too much may promote more oedema. Furthermore, as such patients get better, trans-capillary leakage will decrease and the redistribution problems may effectively operate in reverse. It may therefore important to reduce overall IV fluid and electrolyte provision to permit a net negative sodium and water balance, in order to aid oedema resolution.

In view of the above, prescribing IV fluids for oedematous patients with fluid distribution abnormalities needs experience and early senior review. However, the overall approach is usually to treat any intravascular hypovolaemia as one would for resuscitation, but aim for a negative overall fluid and sodium balance as soon as possible. In severe cases, balance can be assessed by comparing total sodium intake (accounting for all sources including other IV fluids, IV drugs and their diluents) with total losses from urinary measurements and estimates of sodium in other external losses. Excretion should exceed intake.

It is also important to correct any potassium depletion in order to maximize sodium exchange, bearing in mind that plasma potassium is a poor marker of whole body status since it is primarily intracellular. However, when giving relatively generous potassium, careful monitoring for hyperkalaemia is needed, especially as many of these patients have some a degree of renal impairment and catabolic patients also have high endogenous potassium ‘supplies’ from lean tissue breakdown. Hyperchloraemia should also be avoided as it may make mobilization of oedema more difficult by reducing renal perfusion . [18]

Diuretics are generally used with caution since they may reduce circulating blood volume and consideration should always be given as to whether the same net effect on fluid balance might not be achieved through reduction of IV fluids, particularly a reduction in the provision of 0.9% sodium chloride. Twice weekly weighing, when possible, in addition to routine daily clinicalexamination allows oedema mobilization to be assessed .

9.1.2.1 Choice of fluids in patients with redistribution problems

A variety of IV fluid types can be used when prescribing for patients with internal redistribution issues. These include crystalloids, synthetic colloids and albumin, with the latter two choices having the theoretical advantage of greater and more persistent intravascular volume expansion with less promotion of further interstitial oedema than crystalloids. However, as with synthetic colloid and albumin use for resuscitation (see chapter 4), these theoretical advantage may not be realized in practice in patients with intravascular hypovolaemia and high rates of trans-capillary extravasation.

As with both maintenance and resuscitation prescribing, there is the possibility that using 0.9% sodium chloride might promote more sodium and water retention than balanced solutions as well increasing any risks from hyperchloraemia. However, many patients with redistribution issues also have a degree of renal impairment and the use of some balanced solutions may be limited by their existing potassium content etc.. Concentrated (20-25%) sodium poor albumin has also been used in patients with redistribution problems who are oedematous due to sodium and water overload but who still have a plasma volume deficit(44), aiming to draw fluid from the interstitial space into the intravascular space and so promote renal perfusion and excretion of the excess sodium and water. However, this use is highly specialized and decisions on the use of this expensive preparation in these situations is usually confined to senior clinicians.

9.2 Intravenous fluid therapy for replacement and redistribution

The objectives of the clinical evidence reviews for this chapter were to identify the most effective type, volumes and timings of intravenous fluid to use for replacement of deficits or ongoing fluid losses in patients who cannot meet their fluid and electrolyte needs by oral or enteral routes. Three evidence reviews were undertaken for this purpose; as detailed in sections 1.2 (types of fluid) and 1.3 (volume and timings) below.

The GDG were aware that the complexity and heterogeneity of most patients with significant redistribution issues was such that they could not be entered into trials and no evidence reviews were undertaken in relation to this group.

9.3 Types of fluid

Review question: What is the most clinical and cost effective fluid for intravenous fluid replacement in hospitalised patients?

We searched for randomised controlled trials, systematic reviews and cohort studies comparing the intravenous fluids that might be used for replacement of deficits or ongoing losses in admission of general ward areas of UK hospitals. These are detailed in the treatment matrix below with a tick indicating the comparisons that would be included if identified.

Table 41: Matrix of treatment comparisons

	Buffered/ physiological	0.45% NaCl in 5% glucose	Sodium chloride 0.18% in 4% glucose	Alternate Balanced Solution	5% Glucose
Sodium chloride 0.9%	✓	✓	✓	✓	✓
Buffered/ physiological		✓	✓	✓	✓
0.45% NaCl in 5% glucose			✓	✓	✓
Sodium chloride 0.18% in 4% glucose				✓	✓
Alternate Balanced Solution					✓

	Buffered/ physiological	0.45% NaCl in 5% glucose	Sodium chloride 0.18% in 4% glucose	Alternate Balanced Solution	5% Glucose
M					
5% Glucose					

For full details of the review protocol, see section C.5 in Appendix C.

9.3.1 Clinical evidence

No studies meeting the review protocol were identified. See the study selection flow chart in section J.5, Appendix J.

9.3.2 Economic evidence

No economic evidence was identified for this review.

9.4 Volumes and timing of fluid administration

Review questions: What is clinical and cost effectiveness of different volumes of fluid administration in patients requiring fluid replacement for ongoing losses?

What are the most clinical and cost effective timings for the administration of IV fluid replacement for ongoing losses?

We searched for randomised controlled trials, systematic reviews and cohort studies comparing the intravenous fluids detailed in the same treatment matrix as used in Table 41.

For more details see review protocols in section C.5, Appendix C.

9.4.1 Clinical evidence

No studies were identified relevant to either of the review questions.

See also the study selection flow chart in section J.5, Appendix J and excluded studies list in section H.5, Appendix H.

9.4.2 Economic evidence

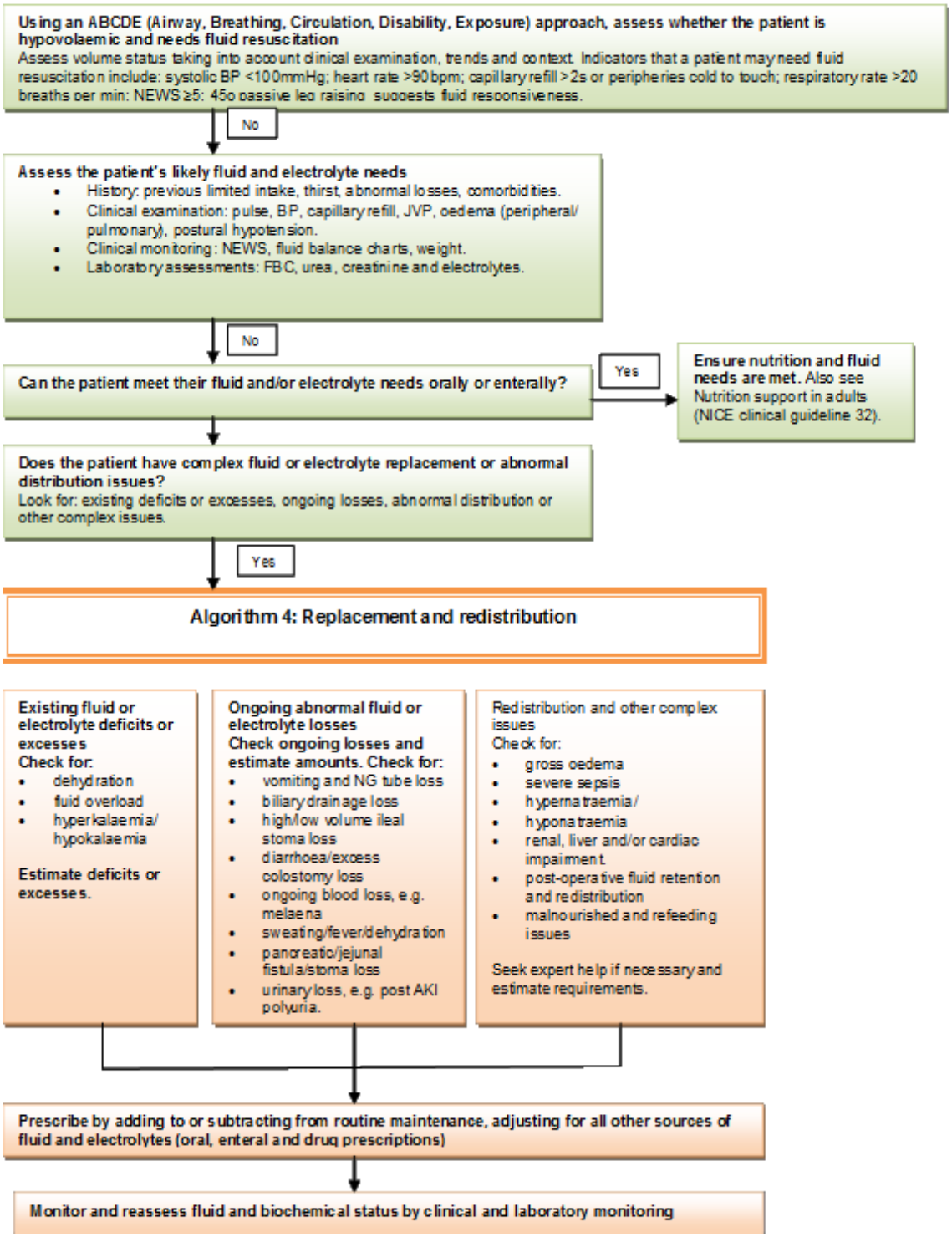
No economic evidence was identified for this review.

9.5 Recommendations and link to evidence

Recommendations	**24. Adjust the IV prescription (add to or subtract from maintenance needs) to account for existing fluid and/or electrolyte deficits or excesses, ongoing losses (see Diagram of ongoing losses) or abnormal distribution.** **25. Seek expert help if patients have a complex fluid and/or electrolyte redistribution issue or imbalance, or significant comorbidity, for example:**

	• **gross oedema** • **severe sepsis** • **hyponatraemia or hypernatraemia** • **renal, liver and/or cardiac impairment** • **post-operative fluid retention and redistribution** • **malnourished and refeeding issues (see Nutrition support in adults [NICE clinical guideline 32]).**
Relative values of different outcomes	The GDG were interested in all cause mortality, length of hospital stay and complications including renal, respiratory and morbidity as measured by SOFA or MODS scores. All cause mortality was considered to be the most important outcome for decision making, although all other outcomes were deemed as important for informing recommendations.
Trade off between clinical benefits and harms	The clinical reviews identified no studies that addressed the best type, volume, timing or rate of fluid to use for intravenous replacement of existing deficits or ongoing abnormal fluid and electrolyte losses. No clinical reviews were undertaken of the best type, volume, timing or rate of fluid to use intravenously for patients with internal fluid redistribution issues since the GDG felt that these patients were too heterogenous and complex to have been entered in trials that would specifically examine these issues in a non-resuscitation context.
Economic considerations	No economic evidence was identified for this review.
Quality of evidence	No evidence was available. The GDG had identified early on that it may not be possible to find RCTs in this topic area. This is because each type of loss would have to be replaced by a type of fluid which addressed the fluid and electrolyte requirements and thus the nature of the intervention does not lend itself to a RCT study design. The recommendations are therefore based on the standard principles of fluid prescribing and the consensus expert opinion of the GDG members.
Other considerations	The recommendations for IV fluid use for replacement and redistribution are based on: • the principles of fluid prescribing described in section 5.1 • the consensus expert views of the GDG. No research recommendations were made in this topic area. The GDG agreed that each type of abnormal ongoing loss would have to be evaluated and replaced with appropriate fluids and electrolytes. A diagram highlighting the different types of abnormal ongoing losses with their constituents was agreed to be useful for purposes of education (see diagram of ongoing losses in section 4.2.2) The GDG discussed the complexity of assessing fluid requirements in patients who have redistribution issues. There was discussion that this was an area where junior doctors were most likely to make errors in judgement and therefore senior review in such patients was crucial. No research recommendation was prioritised in this topic area.

9.5.1 Algorithm 4: Replacement and redistribution


Using an ABCDE (Airway, Breathing, Circulation, Disability, Exposure) approach, assess whether the patient is hypovolaemic and needs fluid resuscitation
Assess volume status taking into account clinical examination, trends and context. Indicators that a patient may need fluid resuscitation include: systolic BP <100mmHg; heart rate >90 bpm; capillary refill >2s or peripheries cold to touch; respiratory rate >20 breaths per min; NEWS ≥5; 45o passive leg raising suggests fluid responsiveness.
No
Assess the patient's likely fluid and electrolyte needs
History: previous limited intake, thirst, abnormal losses, comorbidities.
Clinical examination: pulse, BP, capillary refill, JVP, oedema (peripheral/ pulmonary), postural hypotension.
Clinical monitoring: NEWS, fluid balance charts, weight.
Laboratory assessments: FBC, urea, creatinine and electrolytes.
No
Can the patient meet their fluid and/or electrolyte needs orally or enterally?
Yes
Ensure nutrition and fluid needs are met. Also see Nutrition support in adults (NICE clinical guideline 32).
Does the patient have complex fluid or electrolyte replacement or abnormal distribution issues?
Look for: existing deficits or excesses, ongoing losses, abnormal distribution or other complex issues.
Yes
Algorithm 4: Replacement and redistribution
Existing fluid or electrolyte deficits or excesses
Check for:
dehydration
fluid overload
hyperkalaemia/ hypokalaemia
Estimate deficits or excesses.
Ongoing abnormal fluid or electrolyte losses
Check ongoing losses and estimate amounts. Check for:
vomiting and NG tube loss
biliary drainage loss
high/low volume ileal stoma loss
diarrhoea/excess colostomy loss
ongoing blood loss, e.g. melaena
sweating/fever/dehydration
pancreatic/jejunal fistula/stoma loss
urinary loss, e.g. post AKI polyuria.
Redistribution and other complex issues
Check for:
gross oedema
severe sepsis
hypernatraemia/
hyponatraemia
renal, liver and/or cardiac impairment
post-operative fluid retention and redistribution
malnourished and refeeding issues
Seek expert help if necessary and estimate requirements.
Prescribe by adding to or subtracting from routine maintenance, adjusting for all other sources of fluid and electrolytes (oral, enteral and drug prescriptions)
Monitor and reassess fluid and biochemical status by clinical and laboratory monitoring

This section links the evidence to Algorithm 4 and the recommendation bullet specific to replacement and redistribution.

Recommendations	**Offer IV fluid therapy as part of a protocol (see Algorithms for IV fluid therapy):** • **Assess patients' fluid and electrolyte needs following Algorithm 1: Assessment.** • **If patients need IV fluids for fluid resuscitation, follow Algorithm 2: Fluid resuscitation.** • **If patients need IV fluids for routine maintenance, follow Algorithm 3: Routine maintenance.** • **If patients need IV fluids to address existing deficits or excesses, or ongoing abnormal losses or abnormal fluid distribution, follow Algorithm 4: Replacement and redistribution.**
Relative values of different outcomes	The GDG were interested in all cause mortality, length of hospital stay and complications including renal, respiratory and morbidity as measured by SOFA or MODS scores. All cause mortality was considered to be the most important outcome for decision making, although all other outcomes were deemed as important for informing recommendations.
Trade off between clinical benefits and harms	The clinical reviews identified no studies that addressed the best type, volume, timing or rate of fluid to use for intravenous replacement of existing deficits or ongoing abnormal fluid and electrolyte losses. No clinical reviews were undertaken of the best type, volume, timing or rate of fluid to use intravenously for patients with internal fluid redistribution issues since the GDG felt that these patients were too heteregenous and complex to have been entered in trials that would specifically examine these issues in a non-resuscitation context.
Economic considerations	In section 5.2.4, it was noted that for patients with sepsis, protocolised care was found to be cost-effective for sepsis patients in two studies and cost saving in a third study. Third evidence was considered to be partially applicable and with potentially serious limitations. There was no cost-effectiveness evidence for patients without sepsis. However, given that the health improvements observed in the review of clinical effectiveness evidence were just as pronounced for intra-operative care the GDG felt that the economic benefits of protocols are very likely to be achievable across all settings
Quality of evidence	No evidence was available. The recommendations are based on the standard principles of fluid prescribing and the consensus expert opinion of the GDG members.
Other considerations	Despite the paucity of evidence on the use of protocols for IV fluid administration, the GDG felt that protocolised care in general achieves better outcomes for patients and therefore decided that an algorithmic approach to fluid use for replacement and redistribution was appropriate. In designing the algorithm, the GDG placed particular emphasis on developing recommendations that a foundation year doctor could follow via the protocol to initiate appropriate treatment where possible or to call for senior assistance where necessary. Although the algorithm is targeted at junior doctors, there is an expectation that decision making in these patients is reviewed by seniors. The recommendations and protocol contained within the algorithm on the type, volume, timing and rate of IV fluid use for replacement and redistribution are based on: • the principles of fluid prescribing described in section 5.1 • the reviews of evidence related to the use of algorithms in fluid prescribing described

	in section 5.2 • the consensus expert views of the GDG. This approach allowed the GDG to develop the complete replacement and redistribution algorithm as well as some specific recommendations on IV fluid therapy for replacement and redistribution.

10 Training and education of health care professionals for management of intravenous fluid therapy

10.1 Introduction

Fluid assessment, prescription and administration are essential daily tasks on most medical and surgical wards. These are complex responsibilities that entail careful clinical and biochemical assessment, good understanding of the principles of fluid physiology in health and disease, and appropriate supervision and training.

Unfortunately, problems of both under and over hydration are common and many senior clinicians are aware that there is significant morbidity and mortality associated with inappropriate fluid management in hospitals. The extent of the problem is difficult to quantify as it is often multifactorial and under-reported. However, postoperative over-hydration has been reported in 17-54% of patients and has been shown to prolong hospital stay, to increase morbidity (e.g. pulmonary oedema) and to contribute to about 9000 deaths annually in the USA. Up to 50% of patients, especially older people, have also been reported to develop at least one fluid-related complication due to post-operative over-hydration.

Four key issues, related to failures in education and training, contribute to poor fluid management:

1. ***Poor understanding of the basic principles of fluid balance and a lack of knowledge about fluid management***.

   Although most medical schools address the physiological principles of fluid homeostasis in their undergraduate curricula, these are rarely integrated into practical clinical guidelines to inform fluid prescription by junior doctors in clinical settings. Recent audits report that most junior doctors do not feel adequately prepared to write the fluid prescriptions expected of them at the outset of their clinical careers. The subsequent poor performance has been documented in studies demonstrating no relationship between the fluid balance information available (e.g. serum electrolyte data, input/output charts and daily weights) and the subsequent fluid prescription. There are also data to suggest that less than half of junior doctors know the sodium content of normal saline, and even fewer, the basic daily electrolyte requirements.

   These undergraduate education issues are further compounded by a lack of coordinated postgraduate training. This may be partly attributed to the predominance of 'specialty-requirements' in most training programmes. These often fail to focus on, or assess, basic medical competencies like fluid management, nutrition and pain-control, a problem, recently raised by the Royal College of Physicians. Nursing and paramedical trainees face similar issues and audit suggests that many lack confidence in fluid management. In addition to this lack of formal undergraduate and postgraduate training, junior clinicians and nurses are rarely given guidelines on fluid/electrolyte prescribing or appropriate induction training by their employers.

2. ***Poor fluid balance (chart) documentation.***

   The National Confidential Enquiry into Perioperative Deaths (NCEPOD) in 1999 reported that poor documentation of fluid balance contributed to both morbidity and mortality.[73] Further studies demonstrated that less than half of fluid balance sheets were completed (i.e. no record of oral intake or urine output) and that intravenous fluids were often administered at incorrect rates (which was

often considered to be unimportant)! In addition, less than 10% of staff were aware of the value of monitoring body weight in fluid balance monitoring.

3. ***Poor interpretation of laboratory results***

The interpretation of laboratory results requires considerable expertise with appropriate account made for issues such as the trend in changes of electrolyte levels and the clinical status of the patient. For example the development of hyponatraemia in a patient on IV fluids may reflect whole body sodium depletion from inadequate provision of sodium, particularly in the context of abnormally high sodium losses from thre gastrointestinal tract, but is more often seen in oedematous patients where total body sodium is actually high and the low plasma levels reflect water dilution.

4. ***Inadequate involvement of senior clinicians in fluid management and delegation of fluid prescription to junior members of the team***.

Fluid prescription is often delegated to the least experienced members of the medical team with junior staff responsible for 80% of peri-operative fluid prescriptions. The NCEPOD report ascribed many of the errors in fluid and electrolyte management to inadequate knowledge and training of junior medical staff.[73] It may also indicate that senior clinicians lack confidence in this area, particularly if they did not receive formal fluid management training, and need further education. In the light of the above, it is clear that improvements in education and training related to intravenous fluid therapy are needed and this Chapter seeks to clarify how this might best be achieved.

10.2 Barriers faced by health care professionals

Review question

What are the barriers faced by healthcare professionals in the effective prescription and monitoring of intravenous fluids in hospital settings?

For full details see review protocol in section C.6, Appendix C.

The benefits of a systematic narrative review of clinical evidence in the absence of relevant studies that would show the effect of training and education as a single measurable outcome are highlighted by Oxman and colleagues.[81] This approach has been used previously in national clinical guideline development to great effect (see diagnosis section of NICE Clinical Guideline 61, Irritable Bowel Syndrome). Applying the quality assurance principles advocated by Oxman (1994), a valid review article can, in the absence of interventional clinical evidence, provide the best possible source of information that can lay a foundation for clinical decisions to be made. With regard to this review, the technical team searched broadly for relevant evidence that would enable the GDG to understand what the main issues are with regard to training and education and to inform their interpretation of this evidence when making directive recommendations. The purpose of which is to standardise clinical practice and optimise the experience of patients receiving intravenous fluids through effective training and ongoing education. A strong academic argument can be made that the only way for individual outcomes such as 'barriers faced by healthcare professionals' in relation to education and training to be fully explored and evaluated is through a mixed method approach in the synthesis of available evidence. It is this synthesis that determines both the quality and availability of relevant evidence and provides the GDG with a realistic context for relevant recommendations for clinical practice to be made.

In summary, the absence of randomised studies determines a wider search and yield of relevant literature to provide the best possible source of information for the GDG, for interpretation and decisions to be made. This focused narrative review for individual outcomes as broad as 'training and education' enables an appreciation of relevant literature to be established is more likely to provide valid results, with Oxman et al (1994)[81] stating that it is more useful for clinician interpretation.

10.3 Clinical evidence

We searched for randomised trials comparing the effectiveness of education and training on end patient outcomes in relation to IV fluid management. No trials were identified. The search strategy was therefore purposefully broad, looking at mixed research methods literature relating to 'in-hospital settings' published from 1990 onwards. Ten studies were included in this review and are summarised in the evidence grouping below. The difficulty of determining robust evidence in this review is not dissimilar to other reviews within the guideline, in that the non-clinical setting specific focus of the guideline and the 'all populations' in 'in-hospital settings' focus often determines an implausible approach to normal PICO approaches. What the systematic (by search strategy) narrative review allows is for us to look at the relevant yield and bring evidence summary positions together utilising the mixed research methods published in this relevant area.

Types of study incorporated in this review:

- Survey research (Coombes et al, 2008; Kelly et al, 2011; Chung et al, 2002; Jensen, 2009)[19,21,44,49]
- Knowledge assessment research (Weisgerber et al, 2007)[119]
- Evaluation of training and education research (Dauger et al, 2008; Potts et al,1999; Casserly et al, 2011)[15,24,85]
- Prospective cohort study (Tang and Lee, 2010)[108]
- Action research (Cook, 2005).[20]

10.3.1 Summary of findings

The evidence from the different study designs is presented below with key findings:

10.3.1.1 Survey Research:

Coombes et al, 2008.[21] At the end of medical training, new doctors felt unprepared for fluid prescribing and were concerned about error blame (n=101). This finding supports the GDG consensus of current practice.

Key findings: Lack of adequate clinician preparation with associated potential for increased clinical risk and harm.

Kelly et al, 2011.[49] Interns felt underprepared and lacked confidence in IV fluid management on commencement of their clinical roles (n=52). This again is supportive of GDG consensus of how ill prepared junior doctors are in this important aspect of their role.

Key findings: Lack of adequate clinician preparation with associated potential for increased clinical risk and harm.

Chung et al, 2002.[19] Retrospective review of fluid balance charts (n=250) demonstrated large discrepancy in quality and quantity of fluid balance detail with no clear responsibility across professions

for ownership and termination or recording. This meant that there was no perceived value in relation to benefit and accuracy to inform ongoing decisions. Study participants also raised concerns about the design of fluid balance charts.

Key findings: Poor fluid balance monitoring with associated potential for increased clinical risk and harm.

Jensen, 2009.[44] Survey of nursing graduates following relevant training and education prior to their involvement in intravenous fluid management demonstrated increased confidence and competence in this aspect of their role and care.

Key findings: Increased confidence in relation to IV fluids management following training intervention.

10.3.1.2 Knowledge assessment:

Weisgerber et al, 2007[119] This study was designed to measure competency of fluid management of medical students (M3's) and is illustrative of the concern amongst the GDG. The study was established as an effective knowledge assessment through a combination of multiple choice questions testing cognitive 'know how' and clinical vignette testing the 'know that' aspects of knowledge that support clinical decision making and interpretation of information. The study was considered to be in relevant populations and was reasonably large (n=187). Findings were that the majority of M3s lacked adequate knowledge of fluid management and normal electrolyte physiology. This is interpreted by the GDG as dangerous and could lead to 'harm' rather than 'benefit' in relation to IV fluids management. The recommendation from this study was for a greater emphasis on practice based teaching with immediate feedback and increased formal training to ensure that M3's had the right levels of knowledge and competence when undertaking IV fluid management.

Key findings: Potential for harm or increased clinical risk due to poor knowledge.

10.3.1.3 Evaluation of training and education:

Dauger et al, 2008.[24] Large prospective 'before and after' cohort study (8, 496 as the 'before' comparison and 8,891 patients as 'after' comparison) following introduction of a hypovolaemia protocol. The study demonstrated improved compliance with evidence based hypovolaemia protocol care. Whilst compliance was demonstrated by the study, a lack of follow up data means that we are not able to establish whether initial behaviour change was sustained and protocol led care maintained. Of interest, as this was 'indirect evidence' based in a paediatric population, was that data demonstrated reduced fluid challenge duration compared to standard care (possibly preventing additional problems of fluid overload at a later stage) and the cessation of colloid use in treating the clinical condition of hypovolaemia.

Key findings: Positive impact of training intervention on clinician compliance with protocol led care.

Potts et al,1999.[85] Cohort analytic study assessment of training type in 3rd year medical students with no previous IV fluid management experience (n=89). The primary outcome supported the use of computer based training as an effective method to improve knowledge of prescribing and management of IV fluids. This was again identified as 'of interest' to the GDG but it is noted that it is 'indirect' evidence (paediatric population).

Key findings: Benefit to focussed training strategy, in this case 'computer assisted'.

Casserly et al, 2011.[15] Prospective cohort study (n=106 patients) focussed on implementation of sepsis care from admission to the emergency department (ED), stabilisation (including as a key clinical intervention IV fluids prescribing and management) and transfer to the intensive care unit (ICU). Training interventions supported: reduction in time to fluid administration, vasopressor administration (surrogate marker for volume balance) and time to transfer. Further analysis of the primary outcome data showed continued improvement in the processes of care management, reduction in time in the ED prior to transfer to ICU. Training was targeted at all key staff over a three month period. The data showed that in the last three months of the study, that there was a statistically significant reduction in time to administration of the initial fluids recommended in the protocol and time to catheter insertion. Secondary outcomes showed no change to reducing mortality or total length of stay in hospital, this is most likely to be due to the small study population which was not calculated to try and detect this effect.

Key findings: Positive impact of training intervention on clinician compliance with protocol led care.

10.3.1.4 Prospective cohort study

Tang and Lee, 2010[108]

This was a small study with 25 surgical speciality trainees (12 specialist trainees and 13 foundation year trainees). The aim was to evaluate, in controlled conditions, the junior doctors' ability to accurately assess fluid balance, and by association understand the fluid needs of individual patients. Fluid balance management was assessed using total input and total output calculations across 13 charts, leading to a total of 325 data measures. There was no significant difference across the two groups of doctors. However, the study shows alarming results with cause for concern, that surgical trainee calculations are hugely varied and this has an associated potential for 'harm'. This is reported by the authors acknowledging the limitations of the study as a clinical risk issue that needs to be addressed. They report that the fundamental issue is the lack of relevant education and inconsistent poor documentation.

Key findings: Poor knowledge, poor data collection and documentation.

10.3.1.5 Action research

Cook, 2005[20]

This study was seeking to explore the relationship of role (nursing) to fluid administration and management. It was iterative by nature as the technique used was a focus group discussion with feedback involving nurses on 2 neurosurgical wards. Outcome of the research helped provide greater definition to the role of the nurse and greater certainty with fluid administration and management. The research process in itself improved knowledge and certainty. The roles (themes) that nurses identified, emerging from focus group discussions were:

1. Administration of fluid
2. Assessment of the patient and rationale for treatment (IV fluids)
3. Accurate documentation
4. Evaluation of therapy
5. Appraisal with medical staff in relation to benefit and harm of IV fluids

6. Safe and effective management (safe practice).

Key findings: Improved knowledge led to improved confidence in IV fluid management.

10.4 Evidence summary

Key evidence findings were:

- Lack of adequate clinician preparation is associated with potential for increased clinical risk and harm.
- Poor fluid balance monitoring is associated with potential for increased clinical risk and harm.
- Low confidence in relation to IV fluids management is sub optimal in relation to clinician preparation.
- Poor knowledge is associated to increased potential for harm or increased clinical risk.
- Positive impact of training intervention on clinician compliance with protocol led care.
- Benefit to focussed training strategy, in this case 'computer assisted'.
- Improved knowledge led to improved confidence in IV fluid management.

The following themes were identified from the literature review:

- Understanding of physiology (what you should know prior to prescribing intravenous fluid)
- Initial and ongoing training and education issues
- Assessment of competence in relation to prescribing and administering intravenous fluids
- Intravenous fluids management (protocol led care and prescribing)
- Communication issues.

10.5 Key themes

10.5.1 Understanding off fluid physiology and pathophysiology (what you should know prior to prescribing intravenous fluid)

The assessment, prescription and administration of IV fluids requires an understanding of the basic physiology of fluid and electrolyte homeostasis and the changes that occur with illness or injury.. Although these issues are always part of undergraduate curricula, there is often failure to integrate theoretical knowledge into practical guidelines which inform safe and appropriate IV fluid administration. An understanding of the following basic concepts is required:

- ***Fluid and electrolyte compartments:*** including the volumes of individual compartments, the distribution and movement of electrolytes between compartments and the importance of osmotic pressure and membrane function in health and disease.

- ***Intravascular volume:*** It is essential to understand the determinants of intravascular volume and the roles of and interactions between many factors including: 'oncotic pressure' from large molecular weight (MW), non-diffusible vascular plasma proteins (e.g. albumin); the permeability ('leakiness') of the blood vessels; and circulatory hydrostatic pressure dictated by cardiac function and fluid status. Of particular importance is an understanding of the normal 'albumin cycle' and capillary permeability and their responses to acute pathological conditions and subsequent recovery.

- ***Normal daily fluid losses and renal function and the consequences of disease:*** normal daily fluid and electrolyte losses should be core knowledge, as should be the ability to assess and formulate a

replacement plan for the fluid and electrolyte consequences of disease. This requires a good understanding of the physiological processes controlling fluid and electrolyte homeostasis in health and disease. In particular, the kidneys ability to excrete solute and electrolyte loads during resuscitation in acute illness must be clear.

- ***Response to stress:*** including the endocrine, metabolic and renal responses to acute illness or injury and their effect on salt and water handling should be known and the appropriate management responses to subsequent salt and water retention.
- ***Physiological consequences of chronic disease (e.g. cardiac, renal, endocrine) on fluid and electrolyte management:*** changes in cardiac or urine output, variable ability to excrete solutes and changes in metabolic waste production may have significant effects on fluid management depending on the associated fluid and electrolyte losses, physiological adaptations (e.g. neurohormonal responses) and metabolic effects.
- ***The clinical approaches needed to assess fluid and electrolyte needs for resuscitation, routine maintenance, replacement of deficts/ ongoing losses and redistribution issues, and the importance of reassessment and monitoring The composition and properties of commonly administered intravenous fluids***

Educators and clinicians need to work together to assist trainees and practicing clinicians to address and understand the complex physiological responses that occur during disease processes and how these alter fluid and electrolyte requirements in a clinically relevant problem-solving based approach with appropriate assessment and feed-back.

10.5.2 Initial and ongoing training and education issues

Inadequate knowledge, failure to recognise the importance of fluid management in patient care and a reluctance to take this issue seriously are major factors in poor fluid management. The causes of this lack of engagement are multifactorial, but poor education, training and supervision are major contributors:

- Although medical and nursing undergraduate curricula address most aspects of fluid and electrolyte homeostasis, there is failure to integrate and assess this knowledge in a clinically relevant format.
- Fluid management teaching is included in most Foundation and Core Medical Training programmes but is often unstructured, without a defined curriculum or stated minimum competencies. Knowledge is rarely formally assessed in terms of 'practical' prescription competency (e.g. DOPS) or Membership (e.g. MRCP, FRCS) examinations. Higher specialty programmes tend to focus on the acquisition of 'specialty skills' rather than core medical competencies like fluid management, nutrition and pain management, despite these core competencies having profound effects on specialist outcomes.
- Fluid prescription is often perceived to be less important than other aspects of medical care by junior clinicians and the wider medical team because senior doctors and nurses fail to take responsibility, appear disinterested in, and tend to delegate this role to less senior members of the team without supervision or review.
- Much of the data collection to inform high quality prescription (e.g. fluid input/output charts, daily weights etc.) is ignored by prescribers and results in disillusionment of those tasked with this data collection (i.e. the nursing staff). This leads to poor compliance with the data collection which is subsequently of little value in the fluid status assessment.

- The lack of importance attributed to fluid management is reflected in the lack of adequate research in this field. Poor funding results in inadequate data collection, contradictory findings and conflicts of opinion. Consequently many clinicians are left with the impression that any strategy will do. In the absence of consensus the need for carefully managed research and clinical guidance is even greater and should be a national priority.
- There is a lack of published guidance or national standard setting to inform fluid balance assessment (i.e. input/output chart, electrolyte monitoring) and subsequent fluid prescription (particularly in the absence of clear research findings). As a consequence standards are not reviewed or tested as for other guidelines.
- Morbidity and mortality related to fluid prescription is inadequately monitored or reviewed as it is deemed too difficult to do 'accurately'. Although doctors and nurses are aware of the morbidity associated with over- or under-hydration, it is rarely, if ever, reported as a clinical incident.

Education and training improve clinical assessment, understanding of monitored data (e.g. serum electrolytes, input/output charts), appropriate fluid choice (e.g. crystalloid, colloid) and knowledge of the current literature and can be demonstrated to improve fluid management and patient outcomes. For example, education about the value of conservative (restricted) fluid administration in acute lung injury, many post-operative situations and the recovery phase of critical illness, although still largely unrecognised despite good data demonstrating improved outcomes, has clear benefit. Senior clinicians and nurses must be seen to take fluid management seriously and to provide appropriate leadership and supervision for junior medical colleagues. Senior clinician refresher courses in fluid management should be available.

10.5.3 Assessment of competence in relation to prescribing and administering intravenous fluids

Fluid management competency should be assessed and reviewed throughout training and as part of standard medical clinical governance reviews and the revalidation process.

- Undergraduate training should include formal assessment of a trainees' knowledge of basic fluid and electrolyte physiology and the response to disease, the normal daily fluid and electrolyte requirements in routine medical and post-operative surgical patients and the ability to communicate and prescribe a 24 hour maintenance fluid regime. Resuscitation fluid regimes and the basic principles underlying adjustment of maintenance regimes for ongoing or additional fluid and electrolyte losses or complicating factors should be known. Trainees should be able to demonstrate an ability to collate and interpret monitored data, to recommend an appropriate fluid regime and to complete an appropriate prescription including dates, signatures (and designations), selection of appropriate fluid types, rate of infusion and electrolyte supplements.
- During early medical or nursing training (e.g. Foundation and Core Training Programmes) core generic skills developed during undergraduate training should be 'fine-tuned' and formally assessed in terms of the required 'practical' essential knowledge and 'practical' problem solving prescription competency (e.g. directly observed practical skills, case based discussions). Refinement of the ability to deliver resuscitation fluid regime without associated development of complications (e.g. pulmonary oedema) and adjustment of maintenance regimes for ongoing losses or complicating factors should be developed. Trainees planning specialist training should be encouraged to develop and demonstrate fluid management competencies appropriate to their chosen specialty For example medical trainees would be expected to be familiar with guidelines for fluid management of common acute medical emergencies (e.g. diabetic ketoacidosis, liver failure, acute kidney injury) and surgical trainees with post-operative fluid regimes and adjustments required for ongoing losses (e.g.

nasogastric, fistula). Assessment and demonstration of competency should be required prior to progression to specialty training.

- Specialist trainees and specialty consultants should be able to demonstrate continuing core fluid management competencies. Trainees and consultants involved in acute, general or intensive care medicine or surgery and anaesthetists would be expected to develop further competency in the management of the critically compromised circulation and complex fluid balance problems. Some specialists would be expected to develop expertise and demonstrate proficiency in the management of complex losses (e.g. high output ileal fistulae) or metabolic derangements.

Responsibility for the delivery, assessment and competency review should lie with Medical School Deans, General and Specialty Training Programme Curriculum Committees, the General Medical Council (as part of revalidation) and Nursing Council.

10.5.4 Intravenous fluids management (protocol led care and prescribing)

This part of the review is for minimal guidance only. Please refer to the systematic review and associated recommendations on protocol led care for intravenous fluids management and the four associated algorithms central to this guideline.

Observations from the review of evidence are to determine whether an intravenous fluid is necessary at all, a basic question that needs to be asked as oral or nasogastric fluids are usually always preferable. Intravenous fluid administration is indicated in patients who are:

- acutely unwell and requiring large quantities of fluid for resuscitation
- unable to drink (e.g. unconscious, unsafe swallow (e.g. following strokes, facio-maxillary injury)
- unable to absorb adequate quantities of water (e.g. vomiting, paralytic ileus, diarrhoea)
- losing excessive quantities of fluid (e.g. diarrhoea, haemorrhage, burns)

The basic principles of fluid administration are to:

- Replace normal fluid and electrolyte losses.
- Replenish substantial deficits or ongoing losses.
- Provide additional resuscitation fluids to correct for the effects of underlying pathology.
- Maintain an adequate cardiac output, blood pressure and subsequent peripheral blood flow/distribution of oxygen and other nutrients to satisfy the metabolic needs of body tissues and organs, aid temperature regulation (e.g. sweating) and ensure appropriate removal of carbon dioxide and metabolic waste from the body.
- Ensure a stable cellular and extracellular milieu to preserve cellular transmembrane potentials and normal cellular transport mechanisms for essential ions, respiratory gases, solutes and waste products.
- Avoid excessive oedema which may impair cellular oxygen and nutrient delivery by increasing capillary-to-cell diffusion distances, especially during hypoxaemia.

Prescription of an intravenous fluid should follow a careful clinical assessment, biochemical review and available fluid balance data (e.g. input/output charts, weights). Total fluid and electrolyte requirements, resuscitation needs and other complicating factors should be determined and the most appropriate fluid to provide these requirements determined. Crystalloid and colloid requirements should be prescribed daily and adjusted if enteral feeding is not successful. The type of fluid (i.e. 5% dextrose for water

replacement), electrolyte additives (e.g. potassium) , route and rate of infusion should be prescribed with the date and signature of the issuing physician.

Typically fluid selection is guided by the underlying condition, extracellular fluid status (e.g. oedema), fluid losses (e.g. diarrhoea), renal function, fluid balance (±weight) and electrolyte concentrations. In the absence of normal homeostatic mechanisms, the fluid prescription should address:

- Basic maintenance fluids to replace normal daily water and electrolyte losses (see regular maintenance fluid algorithm).
- Additional resuscitation fluids to replenish potential fluid deficits and to compensate for the underlying pathology and maintain an adequate circulation (see resuscitation algorithm).
- The rate of fluid administration and the time course over which potential fluid and electrolyte deficits should be corrected. This should take into account the rate of development of fluid and electrolyte abnormalities (e.g. established hypo or hypernatraemia should be corrected slowly to avoid potential neurological sequelae like central pontine demyelinoslysis).
- Potential complicating factors including renal, cardiac, hepatic and endocrine function, complex losses (e.g. ileal fistulae), hypoalbuminaemia and peripheral oedema should be addressed (see redistribution fluid algorithm).

In general, the fluid that is lost is replaced. Thus blood is most appropriate for haemorrhagic loss. Replacement fluids should match normal daily losses. However in more complex situations, it may not be appropriate for the replacement fluid to match the perceived deficit (see below). Thus, in acutely unwell patients (e.g. sepsis) and those with renal impairment or complex fluid losses (e.g. burns, fistulae) selection of replacement fluid (e.g. crystalloid, colloid) should be dictated by specialty guidelines (e.g. diabetic ketoacidosis).

10.5.5 Communication issues

Patients should be informed as to why they require intravenous fluids, how long they will require them, timing (i.e. can intravenous infusions be stopped at night to allow better sleep) and potential complications (e.g. phlebitis due to fluid additives like potassium chloride). They should be given the opportunity to relate any relevant information and to discuss their concerns.

Senior healthcare professionals across all disciplines must take responsibility for the assessment of fluid requirements and prescription. Junior colleagues must be adequately supervised, their practice assessed and poor practice challenged to demonstrate that this is an important clinical issue with significant implications for patient outcome. Junior clinicians should be encouraged to discuss the fluid management of their patients with senior colleagues.

All patients on intravenous fluid require monitoring (e.g. biochemistry, input/output charts, weighing). This data should always be reviewed as it enhances fluid management and demonstrates to the team collecting this information that this data is important to patients care. Daily fluid and electrolyte requirements should be carefully assessed and clearly prescribed. Fluid prescriptions written by out-of hours teams who are not familiar with the patient are likely to be inferior and should not be tolerated. Practice should be audited and presented to the wider team to highlight potential problems and adjust practice.

Communication with the nursing team is essential. As the primary carers for intravenous fluid administration/monitoring, with considerable expertise, they should have the opportunity to raise concerns or issues related to fluid management. Appropriate intravenous access should be available. If an intravenous line is not expected to last the 24 hour period it should be replaced during daytime hours

to avoid disturbing the patients sleep and as out-of-hours night-time doctors are often over-stretched risking poor infection control practices.

10.6 Economic evidence

No economic evidence was found for this question.

10.7 Recommendations and link to evidence

Recommendations	**26. Hospitals should establish systems to ensure that all healthcare professionals involved in prescribing and delivering IV fluid therapy are trained on the principles covered in this guideline, and are then formally assessed and reassessed at regular intervals to demonstrate competence in:** • **understanding the physiology of fluid and electrolyte balance in patients with normal physiology and during illness** • **assessing patients' fluid and electrolyte needs (the 5 Rs: Resuscitation, Routine maintenance, Replacement, Redistribution and Reassessment)** • **assessing the risks, benefits and harms of IV fluids** • **prescribing and administering IV fluids** • **monitoring the patient response** • **evaluating and documenting changes and** • **taking appropriate action as required.** **27. Healthcare professionals should receive training and education about, and be competent in, recognising, assessing and preventing consequences of mismanaged IV fluid therapy, including:** • **pulmonary oedema** • **peripheral oedema** • **volume depletion and shock.** **28. Hospitals should have an IV fluids lead, responsible for training, clinical governance, audit and review of IV fluid prescribing and patient outcomes.**
Relative values of different outcomes	Several studies reported that medical and nursing staff lack important knowledge essential for high quality fluid management. In response to these findings and obvious safety implications, there is increasing data to demonstrate the effectiveness of a variety of teaching methods and programmes to improve fluid management knowledge and clinical performance in both medical and nursing practice, not least the benefits of protocol led care (see relevant chapter). In particular simulation training is increasingly recognised as an effective teaching technique that can be combined with competency assessment in a multidisciplinary setting. There is also evidence from reviews of other areas of poor clinical practice (e.g. nutrition) that setting standards can improve outcomes and it is hoped that this guideline will start this process. The recognition that all medical and nursing graduates need minimum levels of competence in fluid management, with some becoming experts in these fields, is long overdue. Training in fluid management must also be embedded in both general and

	specialty training programmes with clear curriculum based teaching objectives and delineation of minimum standards of clinical competency and knowledge for each stage of training and clinical delivery. Recognition and management of the clinical complications of fluid management should also be considered.
Trade-off between clinical benefits and harms	Key evidence findings were: Lack of adequate clinician preparation is associated with potential for increased clinical risk and harm. GDG interpretation to emphasise the importance of normative educative activity at the undergraduate, post graduate and continuing professional development levels. Poor fluid balance monitoring is associated with potential for increased clinical risk and harm. GDG interpretation is for renewed emphasis on the importance of maintaining accurate fluid measurement. Low confidence in relation to IV fluids management is sub optimal in relation to clinician preparation. GDG interpretation is increased emphasis on the value placed on all training and education supporting clinicians to be 'fit for purpose' in relation to assessing, prescribing, managing and evaluating the efficacy of IV fluid support. Poor knowledge is associated to increased potential for harm or increased clinical risk. GDG interpretation is that this evidence supports their experience of practice and must be taken seriously as potential adverse effects of fluid mismanagement. Positive impact of training intervention on clinician compliance with protocol led care. GDG recognise the value of systems supporting education and training activity to optimise patient outcome from IV fluid administration. There is some benefit to focussed training strategy ('computer assisted'). Improved knowledge leads to improved confidence in IV fluid management
Economic considerations	There was no cost-effectiveness evidence for this topic. These recommendations should be implemented through training and quality assurance mechanisms already in place. In the medium to longer term the training should be primarily through undergraduate training. In the short-term there will be some costs incurred in training current staff to the required standard. Costing this is not straightforward because 1) A course could be delivered by many different means (including e-learning), some of which might not take much staff time. 2) The costs may potentially be offset by cost savings through improving practice, which are difficult to estimate (e.g. by preventing complications). Therefore there is an interaction between training and all the other recommendations in the guideline. The NICE implementation team are developing an e-learning tool for this guideline and therefore the training could be delivered through this route without the cost of experts and with a small amount of time from the staff themselves. Although difficult to quantify, the outcome of this guideline should be both substantial health gain and cost savings since the following are recommended: a) the lowest cost fluid for resuscitation b) One of the lowest cost fluids for maintenance but one that more closely meets the patients daily physiological requirements c) the stopping of IV fluids for patients that are able to take oral fluid d) lower volumes of fluid than is currently practiced e) clinicians prescribe IV fluid intake to meet the needs of individual patients so as to reduce adverse events

	f) identification and reporting of the adverse events of mis-prescribing.
Quality of evidence	The quality of evidence is variable throughout this systematic narrative review, acknowledging that there is no randomised evidence supporting this important aspect of training and development. This is not atypical and certainly is not unique to the context of IV Fluid therapy. The value of blending a number of research methods through narrative review is well documented, and importantly supported the GDG to discuss the value placed on training and education activity in three main areas, these are: • The importance of embedding this guidance into the undergraduate curriculum and ensure that it features in exam processes • The importance of embedding this guidance into specialist training programmes and ensure that it features in exam processes • The importance of embedding this guidance in on-going support to qualified and senior clinicians who carry professional and governance responsibility for optimal IV fluid therapy practice and outcomes.
Other considerations	The GDG recognised that there is a pressing need to reinforce both the principles and key aspects of knowledge relating to fluid management in all healthcare curricula The GDG recognise that many aspects of this guideline are about culture shift, and do not underestimate the planning that needs to support this shift. The GDG felt strongly about the importance of the role of the IV fluids lead. There is strong evidence of mismanagement in order to support this recommendation. The recommendation reflects GDG expert view- that this role is possible to establish within existing workforce modelling, and would promote the guidance, best practice across the Trust they are employed by and to review learning from 'near miss' and critical incident reporting. This is crucial in optimising IV fluid therapy as a management intervention. Patient views are consistently strong on the importance of effective engagement of the patient in relation to fluid management needs. With encouragement for the multi-disciplinary team to discuss and clearly communicate the IV fluid management plan Recommendations 25 and 27 were identified as key priorities for implementation by the GDG. Due to the paucity of evidence in this area, the GDG prioritised a research recommendation in this area evaluating the effectiveness of hospital systems that ensure training and education and proper reporting of complications of fluid mismanagement (see section 10.8)

10.8 Research recommendations

6. Does the introduction of hospital systems that ensure:

- **all hospital healthcare professionals involved in prescribing and delivering IV fluid therapy are appropriately trained in the principles of fluid prescribing; and**
- **all IV fluid therapy-related complications are reported;**

lead to a reduction in fluid-related complications and associated healthcare costs?

Why this is important?

Despite the fact that assessment of a patient's IV fluid needs and prescription of an appropriate IV fluid regimen can be complex, the job is often delegated to healthcare professionals with limited experience and little or no relevant training. Errors in prescribing IV fluids and electrolytes are thought to be common and associated with unnecessary morbidity, mortality and increased healthcare costs. The problems are most likely to occur in emergency departments, acute admission units and medical and surgical wards rather than operating theatres and critical care units, since the staff in more general hospital areas have less relevant expertise, and standards of recording and monitoring of IV fluid and electrolyte therapy can be poor. In addition, the consequences of IV fluid mismanagement are not widely reported. It would be useful to undertake this study to evaluate and audit the effects of introducing training and governance initiatives in the NHS.

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12 Acronyms and abbreviations

AAA	Abdominal aortic aneurysm
AKI	Acute kidney injury
APACHE	Acute physiology and chronic health evaluation II
ARDS	Acute respiratory distress syndrome
Ca	Calcium
CABG	Coronary artery bypass graft (surgery)
CAPD	Continuous ambulatory peritoneal dialysis
CCA	Cost-consequences analysis
CEA	Cost-effectiveness analysis
CHF	Congestive heart failure
CI	Confidence interval
Cl	Chloride
COPD	Chronic obstructive pulmonary disease
CRT	Capillary refill time
CVP	Central venous pressure
DBP	Diastolic blood pressure
ECF	Extracellular fluids
ECO	Effective cardiac output
EQ-5D	EuroQol-5D
FINESS	Fluid resuscitation in the management of early septic shock
FIRST	Fluids in resuscitation of severe trauma
GDG	Guideline development group
GRADE	Grading of recommendations assessment, development and evaluation
HES	Hydroxyethyl starch
HR	Heart rate
HRQoL	Health-related quality of life
HTA	Health technology assessment or appraisal
ICER	Incremental cost-effectiveness ratio
ICF	Intracellular fluid
INB	Incremental net benefit
ISF	Interstitial fluid
ISS	Injury severity score
ITBVI	Intra-thoracic blood volume index
ITT	Intention-to-treat analysis
IV	Intravenous
JVP	Jugular venous pressure
K	Potassium
KCl	Potassium chloride
LETR	Linking evidence to recommendations
LVF	Left ventricular failure

MAP	Mean arterial pressure
MID	Minimal important difference
Mmol	Millimole(s)
MODS	Multiple organ dysfunction score
Morbidity	Diseased condition or state
Mortality	Period of life/time
N	Number of patients randomised
NA	Not applicable
NaCl	Sodium chloride
NG	Nasogastric
NCGC	National Clinical Guideline Centre
NEWS	National Early Warning Score
NICE	National Institute for Health and Care Excellence
NISS	New injury severity score
NNT	Numbers needed to treat
NPSA	National Patient Safety Agency
NR	Not reported
NS	Not significant
PICO	Patient, intervention, comparison, outcome
PONV	Post-operative nausea and vomiting
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RR	Relative risk
SA	Sensitivity analysis
SAFE study	Saline versus albumin fluid evaluation
SAP	Severe acute pancreatitis
SBP	Systolic blood pressure
ScvO2	Central venous oxygen saturation
SD	Standard deviation
SE	Standard error
SOFA score	Sequential organ failure assessment score
TA	Technology appraisal
TBI	Traumatic brain injury
VBG	Venous blood gas
UFH	Unfractionated heparin
UNG	Understanding NICE guidance
VBG	Venous blood gases
VISEP	Efficacy of volume substitution and insulin therapy in severe sepsis

13 Glossary

Abstract	Summary of a study, which may be published alone or as an introduction to a full scientific paper.
Acidosis	Accumulation (increase) of acid within the blood and other body tissues. Occurs when pH less than 7.35.
Albumin	Water soluble protein in the blood
Algorithm (in guidelines)	A flow chart of the clinical decision pathway described in the guideline, where decision points are represented with boxes, linked with arrows.
Allocation concealment	The process used to prevent advance knowledge of group assignment in a RCT. The allocation process should be impervious to any influence by the individual making the allocation, by being administered by someone who is not responsible for recruiting participants.
Alternate balanced solutions	Alternate balanced solutions aresolutions having a pH of 4.5, osmolarity of 284 mOsm/l and the following composition of electrolytes (in mmol/l) Sodium: 31, Chloride: 31, Calcium: 0, Potassium: 0 Bicarbonate: 0 Magnesium: 0, Glucose: 222mmol/l. These are available commercially under different brand names.
Anuria	Absence of urine production or output less than 100ml per day. Anuria may be caused by a failure or kidney dysfunction, a decline in blood pressure below that required to maintain filtration pressure in the kidney, or an obstruction in the urinary passages.
Applicability	The degree to which the results of an observation, study or review are likely to hold true in a particular clinical practice setting.
Arm (of a clinical study)	Sub-section of individuals within a study who receive one particular intervention, for example placebo arm
Association	Statistical relationship between two or more events, characteristics or other variables. The relationship may or may not be causal.
Baseline	The initial set of measurements at the beginning of a study (after run-in period where applicable), with which subsequent results are compared.
Before-and-after study	A study that investigates the effects of an intervention by measuring particular characteristics of a population both before and after taking the intervention, and assessing any change that occurs.
Bias	Systematic (as opposed to random) deviation of the results of a study from the 'true' results that is caused by the way the study is designed or conducted.
Bicarbonate	An alkaline molecule, generated in the body from carbon dioxide, and functioning as a reservoir to adjust for increases in acidity from metabolic activity. It prevents the blood from becoming too acidic.
Blinding	Keeping the study participants, caregivers, researchers and outcome assessors unaware about the interventions to which the participants have been allocated in a study.
Carer (caregiver)	Someone other than a health professional who is involved in caring for a person with a medical condition.
Case-control study	Comparative observational study in which the investigator selects individuals who have experienced an event (For example, developed a disease) and others who have not (controls), and then collects data to determine previous exposure to a possible cause.
Case-series	Report of a number of cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (control) group of patients.

Clinical efficacy	The extent to which an intervention is active when studied under controlled research conditions.
Clinical effectiveness	The extent to which an intervention produces an overall health benefit in routine clinical practice.
Clinician	A healthcare professional providing direct patient care, for example doctor, nurse or physiotherapist.
Cochrane Review	The Cochrane Library consists of a regularly updated collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews (reviews of randomised controlled trials prepared by the Cochrane Collaboration).
Cohort study	A retrospective or prospective follow-up study. Groups of individuals to be followed up are defined on the basis of presence or absence of exposure to a suspected risk factor or intervention. A cohort study can be comparative, in which case two or more groups are selected on the basis of differences in their exposure to the agent of interest.
Colloids	A solution which is administered intravenously and acts as a volume expander. It is composed of particles which are not capable of passing through a semipermeable membrane. Examples of colloids include albumin, starches and gelatin.
Comorbidity	Co-existence of more than one disease or an additional disease (other than that being studied or treated) in an individual.
Comparability	Similarity of the groups in characteristics likely to affect the study results (such as health status or age).
Compensate (shock)	First stage of shock, characterised by low blood flow and perfusion.
Concordance	This is a recent term whose meaning has changed. It was initially applied to the consultation process in which doctor and patient agree therapeutic decisions that incorporate their respective views, but now includes patient support in medicine taking as well as prescribing communication. Concordance reflects social values but does not address medicine-taking and may not lead to improved adherence.
Confidence interval (CI)	A range of values for an unknown population parameter with a stated 'confidence' (conventionally 95%) that it contains the true value. The interval is calculated from sample data, and generally straddles the sample estimate. The 'confidence' value means that if the method used to calculate the interval is repeated many times, then that proportion of intervals will actually contain the true value.
Confounding	In a study, confounding occurs when the effect of an intervention on an outcome is distorted as a result of an association between the population or intervention or outcome and another factor (the 'confounding variable') that can influence the outcome independently of the intervention under study.
Congestive heart failure	The inability of the heart to supply sufficient blood flow to meet needs.
Consensus methods	Techniques that aim to reach an agreement on a particular issue. Consensus methods may used when there is a lack of strong evidence on a particular topic.
Control group	A group of patients recruited into a study that receives no treatment, a treatment of known effect, or a placebo (dummy treatment) - in order to provide a comparison for a group receiving an experimental treatment, such as a new drug.
Cost benefit analysis	A type of economic evaluation where both costs and benefits of healthcare treatment are measured in the same monetary units. If benefits exceed costs, the evaluation would recommend providing the treatment.

Cost-consequences analysis (CCA)	A type of economic evaluation where various health outcomes are reported in addition to cost for each intervention, but there is no overall measure of health gain.
Cost-effectiveness analysis (CEA)	An economic study design in which consequences of different interventions are measured using a single outcome, usually in 'natural' units (For example, life-years gained, deaths avoided, heart attacks avoided, cases detected). Alternative interventions are then compared in terms of cost per unit of effectiveness.
Cost-effectiveness model	An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources in order to estimate the costs and health outcomes.
Cost-utility analysis (CUA)	A form of cost-effectiveness analysis in which the units of effectiveness are quality-adjusted life-years (QALYs).
Creatinine	A waste product produced by the body during muscle metabolism and normally excreted in urine. If the creatinine level increases in the blood, this may indicate decreased kidney function
Credible interval	The Bayesian equivalent of a confidence interval.
Crystalloids	A solution which is administered intravenously and acts as a volume expander. It is composed of particles which are capable of passing through a semipermeable membrane. Examples of crystalloids include sodium chloride 0.9% and lactated Ringer's solution.
Decision analysis	An explicit quantitative approach to decision making under uncertainty, based on evidence from research. This evidence is translated into probabilities, and then into diagrams or decision trees which direct the clinician through a succession of possible scenarios, actions and outcomes.
Dehydration	Loss of body water (pure water with no sodium or solutes); is always accompanied by high sodium concentration in the blood (hypernatremia), treatment is water.
Discounting	Costs and perhaps benefits incurred today have a higher value than costs and benefits occurring in the future. Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present.
Dominance	An intervention is said to be dominant if there is an alternative intervention that is both less costly and more effective.
Drop-out	A participant who withdraws from a trial before the end of trial.
Economic evaluation	Comparative analysis of alternative health strategies (interventions or programmes) in terms of both their costs and consequences.
Effect (as in effect measure, treatment effect, estimate of effect, effect size)	The observed association between interventions and outcomes or a statistic to summarise the strength of the observed association.
Effectiveness	See 'Clinical effectiveness'.
Efficacy	See 'Clinical efficacy'.
Electrolyte	Ions in solution that acquire the capacity to conduct electricity; In the context of this guidance the electrolytes evaluated refer to sodium, potassium and chloride.
Enteral	Absorption through gastrointestinal tract (nose (NG), stomach or intestine)
Epidemiological study	The study of a disease within a population, defining its incidence and prevalence and examining the roles of external influences (for example,

	infection, diet) and interventions.
EQ-5D (EuroQol-5D)	A standardised instrument used to measure a health outcome. It provides a single index value for health status.
Euvolemia	Term implying that the individual described appears to have a normal circulatory or blood fluid volume within their body
Evidence	Information on which a decision or guidance is based. Evidence is obtained from a range of sources including randomised controlled trials, observational studies, expert opinion (of clinical professionals and/or patients).
Exclusion criteria (literature review)	Explicit standards used to decide which studies should be excluded from consideration as potential sources of evidence.
Exclusion criteria (clinical study)	Criteria that define who is not eligible to participate in a clinical study.
Expert	In this guideline, the term 'expert' refers to a healthcare professional who has core competencies to diagnose and manage acute illness. These competencies can be delivered by a variety of models at a local level, such as a critical care outreach team, a hospital-at-night team or a specialist trainee in an acute medical or surgical specialty. For more information, see Acutely ill patients in hospital (NICE clinical guideline 50).
Extended dominance	If Option A is both more clinically effective than Option B and has a lower cost per unit of effect, when both are compared with a do-nothing alternative then Option A is said to have extended dominance over Option B. Option A is therefore more efficient and should be preferred, other things remaining equal.
Extrapolation	In data analysis, predicting the value of a parameter outside the range of observed values.
Fistulae	Permanent abnormal passageway between two organs in the body.
Follow-up	Observation over a period of time of an individual, group or initially defined population whose appropriate characteristics have been assessed in order to observe changes in health status or health-related variables.
Generalisability	The extent to which the results of a study based on measurement in a particular patient population and/or a specific context hold true for another population and/or in a different context. In this instance, this is the degree to which the guideline recommendation is applicable across both geographical and contextual settings. For instance, guidelines that suggest substituting one form of labour for another should acknowledge that these costs might vary across the country.
Gold standard .	See 'Reference standard'
GRADE / GRADE profile	A system developed by the GRADE Working Group to address the shortcomings of present grading systems in healthcare. The GRADE system uses a common, sensible and transparent approach to grading the quality of evidence. The results of applying the GRADE system to clinical trial data are displayed in a table known as a GRADE profile.
Haemodynamic	Related to circulation of blood in the body
Harms	Adverse effects of an intervention.
Health economics	The study of the allocation of scarce resources among alternative healthcare treatments. Health economists are concerned with both increasing the average level of health in the population and improving the distribution of health.
Health-related quality of life (HRQoL)	A combination of an individual's physical, mental and social well-being; not merely the absence of disease.
Heterogeneity Or lack of	The term is used in meta-analyses and systematic reviews when the results or

homogeneity.	estimates of effects of treatment from separate studies seem to be very different – in terms of the size of treatment effects or even to the extent that some indicate beneficial and others suggest adverse treatment effects. Such results may occur as a result of differences between studies in terms of the patient populations, outcome measures, definition of variables or duration of follow-up.
Hypercalcaemia	Increased calcium level in blood
Hyperchloraemia	Increased chloride level in blood
Hyperkalaemia	Increased potassium level in blood
Hypernatraemia	Increased sodium level in blood
Hyperperfusion	Increased blood flow through an organ
Hypervolaemia	Term implying that the individual described appears to have increased circulatory or blood fluid volume within their body
Hypoperfusion	Decreased blood flow through an organ
Hypocalcaemia	Decreased calcium level in blood
Hypochloraemia	Decreased chloride level in blood
Hypokalaemia	Decreased potassium level in blood
Hyponatraemia	Decreased sodium level in blood
Ileal fistula	Abnormal communication between the ileum and another organ or cavity.
Ileus	Intestinal obstruction; maybe characterised by sudden pain, constipation, abdominal distension, persistent faecal vomiting and collapse.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of effect.
Inclusion criteria (literature review)	Explicit criteria used to decide which studies should be considered as potential sources of evidence.
Incremental analysis	The analysis of additional costs and additional clinical outcomes with different interventions.
Incremental cost	The mean cost per patient associated with an intervention minus the mean cost per patient associated with a comparator intervention.
Incremental cost effectiveness ratio (ICER)	The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest for one treatment compared with another.
Incremental net benefit (INB)	The value (usually in monetary terms) of an intervention net of its cost compared with a comparator intervention. The INB can be calculated for a given cost-effectiveness (willingness to pay) threshold. If the threshold is £20,000 per QALY gained then the INB is calculated as: (£20,000 x QALYs gained) – Incremental cost.
Indirectness	The available evidence is different to the review question being addressed, in terms of PICO (population, intervention, comparison and outcome).
Inotropes	Drugs affecting muscle contraction, especially heart muscle
Insensible (water) loss	The amount of fluid lost on a daily basis from the lungs, skin, respiratory tract, and water excreted in the faeces.
Intention to treat analysis (ITT)	A strategy for analysing data from a randomised controlled trial. All participants are included in the arm to which they were allocated, whether or not they received (or completed) the intervention given to that arm. Intention-to-treat analysis prevents bias caused by the loss of participants, which may disrupt the baseline equivalence established by randomisation and which may reflect non-adherence to the protocol.
Intercellular	Space between cells

Interstitial	Lying in between or placed within an organ or tissue.
Intervention	Healthcare action intended to benefit the patient, for example, drug treatment, surgical procedure, psychological therapy.
Kappa statistic	A statistical measure of inter-rater agreement that takes into account the agreement occurring by chance.
Lactic acidosis	Accumulation of lactic acid in the blood; lactic acid is formed in the body during muscular activity by breakdown of glycogen and may be formed at a faster rate when there is inadequate oxygenation of tissues (for example, in sepsis or shock). This is usually estimated by the measurement of lactate levels in venous blood (venous lactate).
Length of stay	The total number of days a patient stays in hospital.
Licence	See 'Product licence'.
Life-years gained	Mean average years of life gained per person as a result of the intervention compared with an alternative intervention.
Likelihood ratio	The likelihood ratio combines information about the sensitivity and specificity. It tells you how much a positive or negative result changes the likelihood that a patient would have the disease. The likelihood ratio of a positive test result (LR+) is sensitivity divided by 1- specificity.
Long-term care	Residential care in a home that may include skilled nursing care and help with everyday activities. This includes nursing homes and residential homes.
Markov model	A method for estimating long-term costs and effects for recurrent or chronic conditions, based on health states and the probability of transition between them within a given time period (cycle).
Meta-analysis	A statistical technique for combining (pooling) the results of a number of studies that address the same question and report on the same outcomes to produce a summary result. The aim is to derive more precise and clear information from a large data pool. It is generally more reliably likely to confirm or refute a hypothesis than the individual trials.
Multivariate model	A statistical model for analysis of the relationship between two or more predictor (independent) variables and the outcome (dependent) variable.
Number needed to treat (NNT)	The number of patients that who on average must be treated to prevent a single occurrence of the outcome of interest.
Observational study	Retrospective or prospective study in which the investigator observes the natural course of events with or without control groups; for example, cohort studies and case–control studies.
Odds ratio	A measure of treatment effectiveness. The odds of an event happening in the treatment group, expressed as a proportion of the odds of it happening in the control group. The 'odds' is the ratio of events to non-events.
Oedema	Excessive fluid in/around cells
Oliguria	Reduced secretion of urine
Opportunity cost	The loss of other health care programmes displaced by investment in or introduction of another intervention. This may be best measured by the health benefits that could have been achieved had the money been spent on the next best alternative healthcare intervention.
Outcome	Measure of the possible results that may stem from exposure to a preventive or therapeutic intervention. Outcome measures may be intermediate endpoints or they can be final endpoints. See 'Intermediate outcome'.
P-value	The probability that an observed difference could have occurred by chance, assuming that there is in fact no underlying difference between the means of the observations. If the probability is less than 1 in 20, the P value is less than

	0.05; a result with a P value of less than 0.05 is conventionally considered to be 'statistically significant'.
Parenteral	Denotes any medication route other than through the alimentary canal, such as intravenous, subcutaneous, intramuscular or mucosal. Parenteral nutrition refers to the provision of caloric needs of a patient by intravenous route who is unable to take food orally.
Passive leg raising	Passive leg raising is a bedside method to assess fluid responsiveness in a patient. It is undertaken by lying the patient flat and passively raising their legs to greater than 45 degrees. If, at 30-90 seconds, the patient shows signs of haemodynamic improvement, it indicates that volume replacement may be required. If the condition of the patient deteriorates, in particular breathlessness, it indicates that the patient may be fluid over loaded.
Perfusion	Passage of fluid through organs or spaces.
Perioperative	The period from admission through surgery until discharge, encompassing the pre-operative and post-operative periods
pH	The acid-alkaline balance
Placebo	An inactive and physically identical medication or procedure used as a comparator in controlled clinical trials
Polypharmacy	The use or prescription of multiple medications
Polyuria	Excessive secretion and discharge of urine
Pontine demyelinosis	Brain cell dysfunction caused by the destruction of the myelin layer covering nerve cells in the middle of the brainstem (pons).
Postoperative	Pertaining to the period after patients leave the operating theatre, following surgery
Power (statistical)	The ability to demonstrate an association when one exists. Power is related to sample size; the larger the sample size, the greater the power and the lower the risk that a possible association could be missed.
Preoperative	The period before surgery commences.
Primary care	Healthcare delivered to patients outside hospitals. Primary care covers a range of services provided by general practitioners, nurses, dentists, pharmacists, opticians and other healthcare professionals.
Primary outcome	The outcome of greatest importance, usually the one in a study that the power calculation is based on.
Product licence	An authorisation from the MHRA to market a medicinal product.
Prognosis	A probable course or outcome of a disease. Prognostic factors are patient or disease characteristics that influence the course. Good prognosis is associated with low rate of undesirable outcomes; poor prognosis is associated with a high rate of undesirable outcomes.
Prospective study	A study in which people are entered into the research and then followed up over a period of time with future events recorded as they happen. This contrasts with studies that are retrospective.
Protocol	A pre-defined set of methods or procedures usually including a treatment plan.
Publication bias	Also known as reporting bias. A bias caused by only a subset of all the relevant data being available. The publication of research can depend on the nature and direction of the study results. Studies in which an intervention is not found to be effective are sometimes not published. Because of this, systematic reviews that fail to include unpublished studies may overestimate the true effect of an intervention. In addition, a published report might present a biased set of results (e.g. only outcomes or sub-groups where a

	statistically significant difference was found.
Quality of life	See 'Health-related quality of life'.
Quality-adjusted life year (QALY)	An index of survival that is adjusted to account for the patient's quality of life during this time. QALYs have the advantage of incorporating changes in both quantity (longevity/mortality) and quality (morbidity, psychological, functional, social and other factors) of life. Used to measure benefits in cost-utility analysis. The QALYs gained are the mean QALYs associated with one treatment minus the mean QALYs associated with an alternative treatment.
Randomisation	Allocation of participants in a research study to two or more alternative groups using a chance procedure, such as computer-generated random numbers. This approach is used in an attempt to ensure there is an even distribution of participants with different characteristics between groups and thus reduce sources of bias.
Randomised controlled trial (RCT)	A comparative study in which participants are randomly allocated to intervention and control groups and followed up to examine differences in outcomes between the groups.
RCT	See 'Randomised controlled trial'.
Receiver operated characteristic (ROC) curve	A graphical method of assessing the accuracy of a diagnostic test. Sensitivity Is plotted against 1-specificity. A perfect test will have a positive, vertical linear slope starting at the origin. A good test will be somewhere close to this ideal.
Reference standard	The test that is considered to be the best available method to establish the presence or absence of the outcome – this may not be the one that is routinely used in practice.
Relative risk (RR)	The number of times more likely or less likely an event is to happen in one group compared with another (calculated as the risk of the event in group A/the risk of the event in group B).
Reporting bias	See publication bias.
Resource implication	The likely impact in terms of finance, workforce or other NHS resources.
Retrospective study	A retrospective study deals with the present/ past and does not involve studying future events. This contrasts with studies that are prospective.
Review question	In guideline development, this term refers to the questions about treatment and care that are formulated to guide the development of evidence-based recommendations.
Secondary outcome	An outcome used to evaluate additional effects of the intervention deemed a priori as being less important than the primary outcomes.
Selection bias	A systematic bias in selecting participants for study groups, so that the groups have differences in prognosis and/or therapeutic sensitivities at baseline. Randomisation (with concealed allocation) of patients protects against this bias.
Sepsis	A severe illness caused by pathogenic organisms or their toxins.
Sensitivity	Sensitivity or recall rate is the proportion of true positives which are correctly identified as such. For example in diagnostic testing it is the proportion of true cases that the test detects. See the related term 'Specificity'
Sensitivity analysis	A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows for exploring the generalisability of results to other settings. The analysis is repeated using different assumptions to examine the effect on the results. One-way simple sensitivity analysis (univariate analysis): each parameter is varied individually in order to isolate the consequences of each parameter on

	the results of the study. Multi-way simple sensitivity analysis (scenario analysis): two or more parameters are varied at the same time and the overall effect on the results is evaluated. Threshold sensitivity analysis: the critical value of parameters above or below which the conclusions of the study will change are identified. Probabilistic sensitivity analysis: probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (For example, Monte Carlo simulation).
Shock	A medical emergency in which the organs and tissues are not receiving an adequate flow of blood. This deprives the organs and tissues of oxygen and allows the build up of waste products; shock can result in serious damage or even death.
Significance (statistical)	A result is deemed statistically significant if the probability of the result occurring by chance is less than 1 in 20 ($p < 0.05$).
Skin turgor	An abnormality in the skin's ability to change shape and return to normal
Specificity	The proportion of true negatives that a correctly identified as such. For example in diagnostic testing the specificity is the proportion of non-cases incorrectly diagnosed as cases. See related term 'Sensitivity'. In terms of literature searching a highly specific search is generally narrow and aimed at picking up the key papers in a field and avoiding a wide range of papers.
Stakeholder	Those with an interest in the use of the guideline. Stakeholders include manufacturers, sponsors, healthcare professionals, and patient and carer groups.
Stoma	An opening either natural or surgical which connects a portion of the body cavity to the outside.
Subcutaneous	For injection, refers to beneath the skin.
Systematic review	Research that summarises the evidence on a clearly formulated question according to a pre-defined protocol using systematic and explicit methods to identify, select and appraise relevant studies, and to extract, collate and report their findings. It may or may not use statistical meta-analysis.
Systemic circulation	Circulation to the whole body
Tachycardia	Increased heart rate
Tachypnoea	Rapid breathing i.e. more than 20 breaths per minute (normal rate is 12-20 per minute).
Time horizon	The time span over which costs and health outcomes are considered in a decision analysis or economic evaluation.
Treatment allocation	Assigning a participant to a particular arm of the trial.
Univariate	Analysis which separately explores each variable in a data set.
Utility	A measure of the strength of an individual's preference for a specific health state in relation to alternative health states. The utility scale assigns numerical values on a scale from 0 (death) to 1 (optimal or 'perfect' health). Health states can be considered worse than death and thus have a negative value.
Volume depletion	State of vascular instability characterized by decreased sodium and water in the extracellular space; causes include vomiting, excessive sweating, diarrhoea, burns, diuretic use and kidney failure.